PREBIOTIC INSPIRATION TO FUNCTIONAL APPLICATION: SYNTHETIC AND MECHANISTIC INVESTIGATIONS OF GLYOXYLATE AND ITS FORMAL DIMER DIHYDROXYFUMARIC ACID

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PREBIOTIC INSPIRATION TO FUNCTIONAL APPLICATION: SYNTHETIC AND MECHANISTIC INVESTIGATIONS OF GLYOXYLATE AND ITS FORMAL DIMER DIHYDROXYFUMARIC ACID

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LIST OF ABBREVIATIONS

Bn – Benzyl

BRSM – Based on Recovered Starting Material

CA – Cyanuric Acid

CCE – Center for Chemical Evolution

COSY – Correlation Spectroscopy

COX – Cyclooxygenase

DBU – 1,8 Diazabicyclo (5.4.0) undec-7-ene

DCE – 1,2 Dichloroethane

DCM – Dichloromethane

DEPT – Distortion less Enhancement by Polarization Transfer

DES – Deep Eutectic Solvent

DHF – Dihydroxy Fumaric Acid

DIBAL – Diisobutylaluminum Hydride

DMAP – 4-Dimethyl Amino Pyridine

DMF – Dimethyl Formamide

DMSO – Dimethyl Sulfoxide

DMT – Dimethoxy trityl

DNA – Deoxyribonucleic Acid

EWG – Electron Withdrawing Group

EtOAc – Ethyl Acetate

GNA – Glycerol Nucleic Acid

HMBC – Heteronuclear Multiple Bond Correlation

HOMO – Highest Occupied Molecular Orbital

LAH – Lithium Aluminum Hydride

LHMDS – Lithium hexamethyl Disilazane

LUMO – Lowest Unoccupied Molecular Orbital

Me – Methyl

MS – Mass Spectrometry

NMR – Nuclear Magnetic Resonance

NSF – National Science Foundation

PNA – Peptide Nucleic Acid

pTSA – Para-toluene Sulfonic Acid

RNA – Ribonucleic Acid

TAP – Triamino Pyridine

TBA – Tetrabutylammonium

TBDPS – Tert-butyl Diphenyl silyl

TBS – Tert-butyl dimethyl silyl

TEA – Triethylamine

TES – Triethyl silyl

THF – Tetrahydrofuran

TLC – Thin Layer Chromatography

Ts – Tosyl

UV – Ultraviolet

CHAPTER 1 INTRODUCTION

1.1 Origin of Life

The question of the origin of life has been one of the great mysteries that man has pondered throughout history. For many years this has been the realm of religion and myth. As the Enlightenment and the growth of science as fundamental discipline advanced people began to try to determine how life as we know it came into being through scientific inquiry and study. One of the first and arguably the most famous of these early origin of life scientists was Charles Darwin. In his work "Origin of Species" he laid out the theory that life can slowly, through natural selection, evolve into more complicated and specialized life. This theory of evolution became the central theory as to how extant life was formed.

In the following decades the understanding of what makes up life exploded. As more discoveries were made, it was understood that life was more and more complicated. All living things are made up of small components that were called cells because they looked like prison cells in the first microscopes. Then it was learned that that there can be living things that are made up of only a single cell. The question then became what makes up a cell? Scientists began to realize that there was need to move beyond simply studying life or biology and toward how chemicals that make up life interact. Thus, biochemistry as field became a major source of study.

Through a long and arduous process, the four main components of life were determined: proteins, nucleic acids, saccharides and lipids (Figure 1). From a relatively small selection of monomer units the wide array of different polymers is made which are used by life to perform all the necessary functions to maintain it. Even while the vast

complexities of how these different biomacromolecules interact and function another set of questions began to arise.

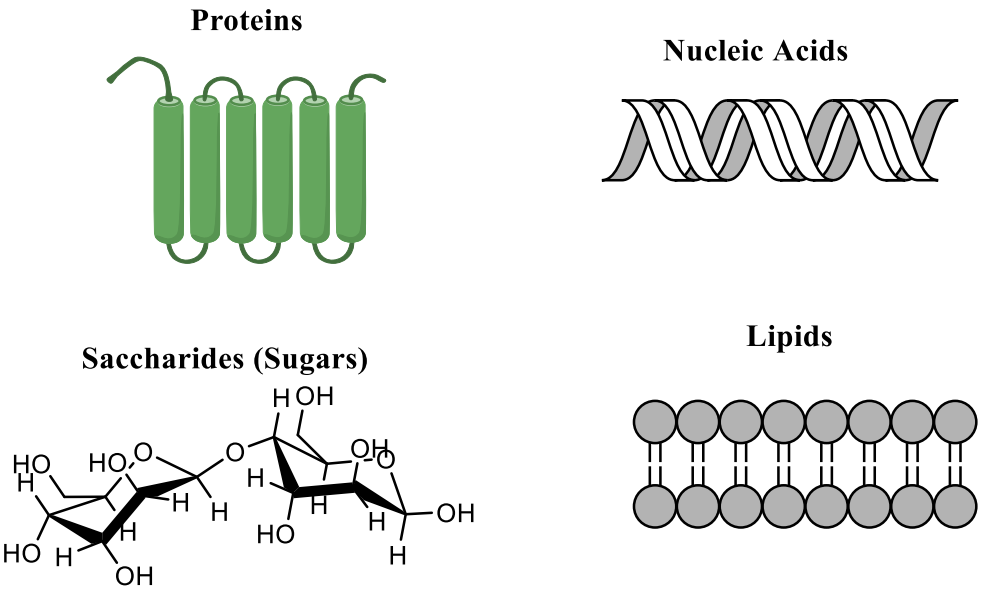


Figure 1 Biomacromolecules of Life

With these linear polymers, the sequence of monomers has been shown to be extremely critical and small changes vastly disrupt or prevent the proper function. Extant biology and biochemistry use complex combinations of all the biomacromolecules to control and direct their own synthesis. The proper sequence of amino acids to make functional proteins is encoded in DNA. The DNA must be copied by other proteins into RNA so that the sequence can be read by other proteins to synthesize the protein that that particular part of RNA codes. This interconnection of DNA-RNA-Proteins is known as the Central Dogma (Figure 2).

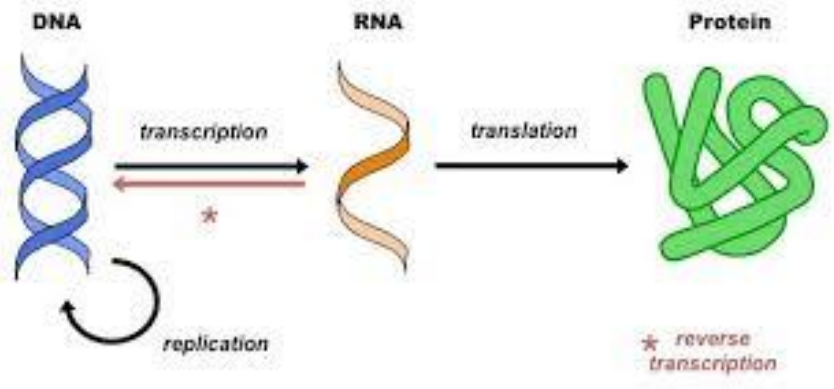


Figure 2 Central Dogma[1]

Through the expounding of this and other key aspects of biochemistry people began to ask how were these complex biomacromolecules were formed on earth before life existed. The general assumption is that because life is made up of biomacromolecules they must have been formed on the early Earth and come together spontaneously to create the first lifeforms or early cells. Answering this new question of "what came before life to make life?" grew into a field of chemistry known as "origin of life" or prebiotic chemistry. This began the study of chemical evolution; how the first biomolecules of life were selected or evolved toward the formation of the first living cells.

1.2 Beginnings of Prebiotic Chemistry

Within this field there are a range of problems that have been and are still being studied. These stretch from what actually was the early Earth like on a physical level to why the polymers that we see in life today were the ones that were selected over similar polymers that could and, in all likelihood, did exist?[2] Was the Earth dry and hot or cold and wet? Did all the reactions occur in the atmosphere with lightning as the source of energy or near boiling hot hydrothermal vents at the floor of oceans? How were the complex monomers formed required to make life? Nucleic acids, amino acids, and sugars

look simple to us today but when trying to form them with no enzyme or specific catalyst it has been seen that there will be many more similar compounds formed that are not seen in life alongside extant species.

Two of the most foundational works that sparked the origin of life field were performed by Albert Eschenmoser and Stanley Miller. Eschenmoser was focused on DNA and the formation of ribose and phosphorylated ribose.[3] The formation of ribose via the formose reaction was combined with phosphorylated glyceraldehyde to show that phosphorylated ribose could be formed along with the other sugars seen through this reaction. This phosphorylated ribose would have been a key intermediate in the formation of nucleotide polymers or DNA. Another key addition by Eschenmoser was the suggestion of the so-called "glyoxylate scenario".[4]

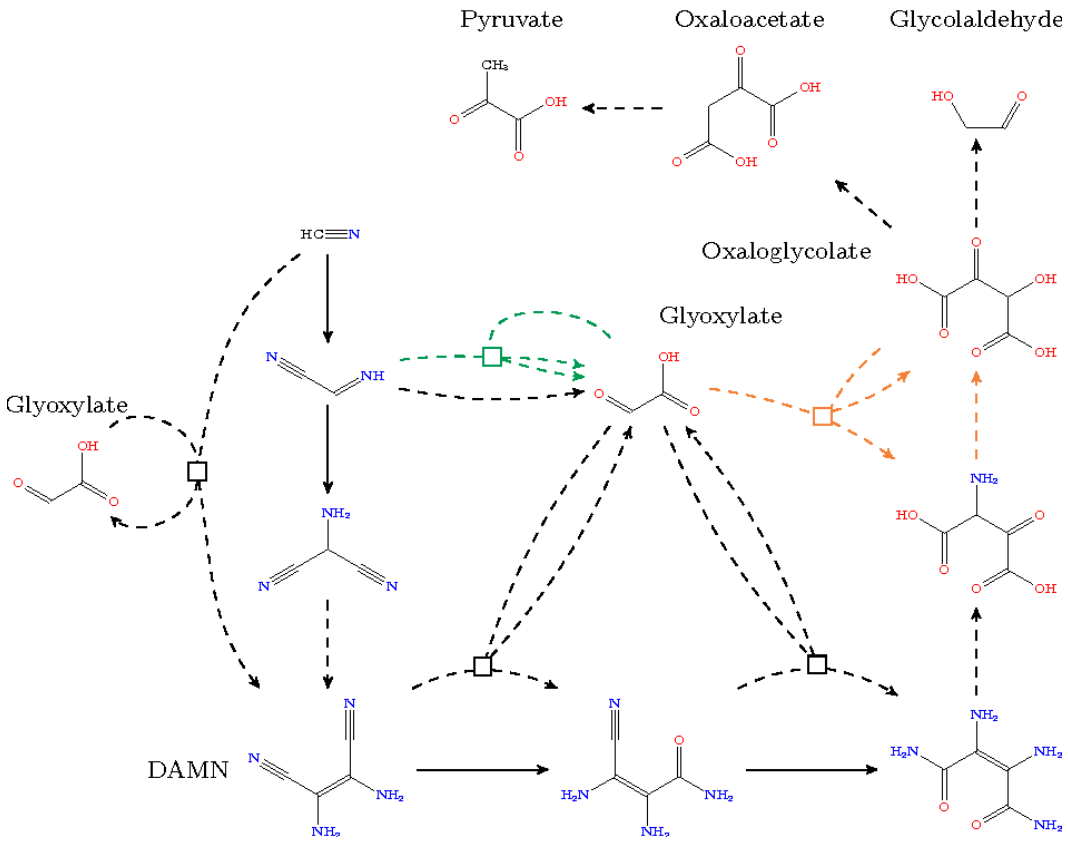


Figure 3 Glyoxylate Scenario[5]

He hypothesized that glyoxylate and the formal dimer dihydroxyfumaric acid (DHF) could have served as part of the prebiotic metabolism to form the monomers of all biomacromolecules (Figure 3). Sugars could more easily be made via the glyoxylate

scenario because unlike the formose scenario only linear sugars can be formed in this fashion.

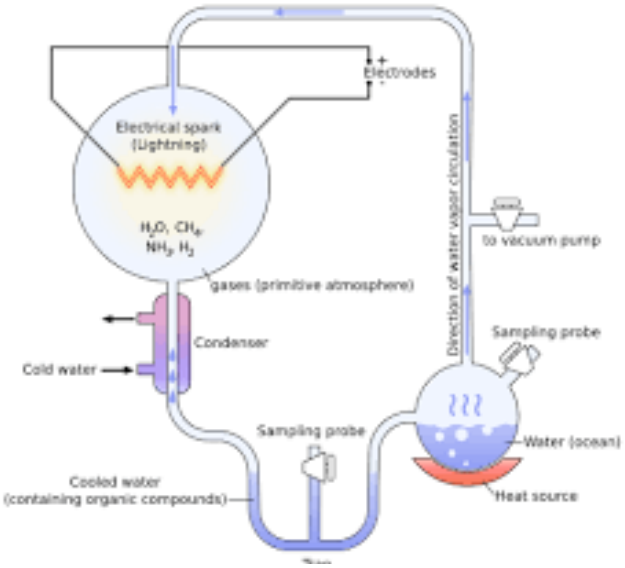


Figure 4 Miller-Urey Experiment

The so-called Miller-Urey experiment (Figure 4) was envisioned as a way to model the early earth atmosphere and study what types of more complex molecules would come from it.[6,7] They modeled the hydrosphere with water evaporating and being mixed with gases believed to be present such as CO_2, CH_4, and N_2. Electricity was introduced through a spark discharge to model lighting and after hours a wide mixture of amino acids, hydroxy acids, and other compounds were seen. This was an important result as it was the first attempt to model the early earth environment to show molecules of life. Further experiments to model volcanic eruptions and sulfur rich spark discharges expanded on this work to show even more interesting molecules.[8] From these starting points along with other leaders such as Oparin with his book "The Origin of Life" the origin of life chemistry field expanded into the expansive universe existing today.

1.3 Center for Chemical Evolution

The work reported in this thesis was performed with the Center for Chemical Evolution (CCE). NSF funds nine large Centers for Chemical Innovation to fund an interinstitutional group that is focused on investigating and hopefully solving great questions in chemistry. The CCE is also jointly funded by NASA with the powerful interest in xenobiology can relate very closely with studying how life began on this planet. There are currently 21 PIs with 43 students and postdocs. Researchers are spread over 7 locations throughout the country from Georgia Tech and Furman all the way across to Scripps Research Institute. The center was founded in 2010. The main goal of the CCE is to determine what the inventory of small molecules present on the early earth could have been and exhibit how this milieu of small molecules in prebiotic earth conditions could self-assemble into polymers that approximate RNA and proteins. There are three main thrusts to the center: modeling and studying novel prebiotic reactions and experiments, developing methods to study the complex mixtures generated by these experiments, and finally taking the wide range of novel chemistries discovered to advance the fundamental understanding in various fields of chemistry.

Research in the CCE is divided into four main themes: proto-nucleic acids, proto-polysaccharides, proto-polypeptides, and alternate environments/building blocks. Each of these focus on one of the major questions in the origin of life field. The first three are investigating methods to possibly form three major extant biopolymers. These are not simply trying to form the exact extant biopolymers but include investigating related polymers that may have been more easily formed. The proto-nucleic acids theme is very interested in alternative nucleobases such as triaminopyrimidine and cyanuric acid (Figure

5)[9] that are able to self-assemble into rosettes that mimic the base pairing of extant nucleobases.

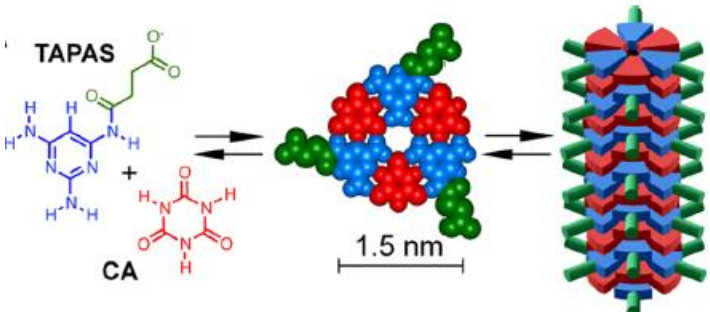


Figure 5: Example of Rosette Assembly

These alternative bases also have the advantage of exhibiting much higher reactivity toward nucleosidation with sugars which has been a major problem in the origin of DNA. The Proto-polysaccharides theme is studying the polymerization of various sugars. The wide range of differing but very structurally similar oligomers that can form between sugars has led the prebiotic organic chemists to partner with analytic chemists to develop new NMR and MS methods to characterize these highly complex mixtures. The Proto-polypeptides theme has found that while amino acids will not spontaneously oligomerize because of the cyclic dimer's high stability, the addition of hydroxy acids has allowed for the polymerization of amino acids with caps of hydroxy acids prevent cyclization.[10]

The fourth theme is mainly focused on the best models for early earth conditions that could have assisted as well as studying the formation of monomeric building blocks for each of the biopolymers. This spans from developing prebiotically plausible eutectic solvents, that have been shown to assist in characterizing depsipeptide sequences,[11] to overcome the strand inhibition problem with high viscosity solvents,[12] and to investigate

prebiotic proto-metabolic cycles.[13] While these themes are focused on differing targets there is significant cross-talk between each of them. The Proto-nucleic Acid theme is looking into formation of DNA has to work with the polysaccharide theme to understand the chemistry of sugars as that is essential to the formation of DNA and related nucleoside polymers. Each of the three polymers these must work with the Environment/Building Block theme to know what monomers and conditions would reasonably be available on the prebiotic earth so that experiments can be done properly.

1.4 Foundation of Current Thesis

These functional applications have taken different forms from the work performed in the CCE. With the attempts to study complex mixtures of monomers new analytical techniques have been necessary. The Fernandez lab has been instrumental in generating new instrumental techniques to study depsipeptides and oligosaccharides by mass spectrometry.[9] Alternatively, the origin of life work has led to new understanding of fundamental properties of materials. The Hud lab was at first interested in finding nucleobases that could have predated extant nucleobases.[9,14] During this investigation it was found that some of the nucleobases could assemble to form long stacked chains that exist as hydrogels (Figure 5). This discovery both led them toward a possible precursor to DNA but also to expand the science of non-covalently linked polymers and hydrogel formation. Nucleobase stacks that were found were some of the most sensitive to changes in pH ever found.

Throughout much of the CCE work certain molecules have popped up again and again in different areas of interest. One such molecule is glyoxylate. Glyoxylate and its formal dimer, dihydroxyfumaric acid (DHF) was initially proposed by Eschenmoser

through the "glyoxylate scenario" and has rapidly been gaining traction as a useful prebiotic building block in a range of different applications.[3] Early work suggested that it could have served as prebiotic precursor to phosphate in the linking of nucleosides together to form DNA analogs. Alongside this, glyoxylate has been studied to possibly serve as a prebiotic source of sugars and other biologic small molecules.

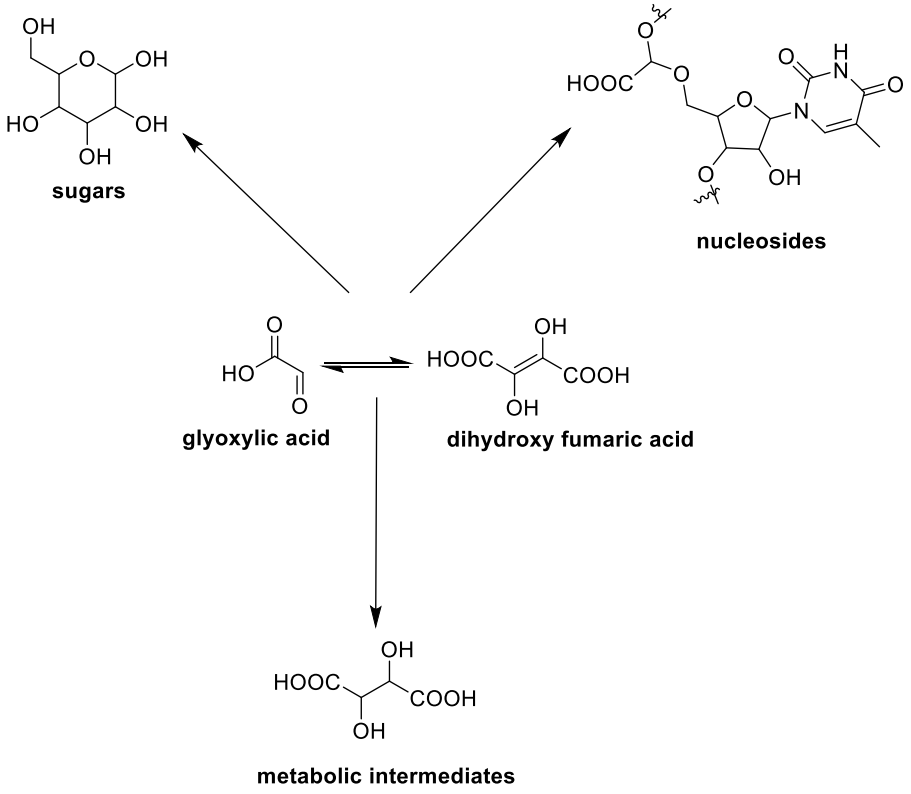


Figure 6: Overview of Thesis Work

These new chemistries and applications thereof show the work being done is useful beyond a curiosity is the focus of this thesis (Figure 6). The work presented herein is dually focused, both trying to synthesize material to study for their prebiotic interest as well as applying the reactions to broader synthetic methodologies. Prebiotic nucleoside and DNA models are a portion of the study. Specifically of interest is trying to solve the phosphorylation problem by replacing the phosphodiester bond with a more prebiotically

plausible glyoxylate linkage. Other studies involve trying to synthesize sugar acids to model a long sugar acid that could have served a precursor to ribose in DNA. Finally, in a purely application and fundamental chemistry focus, recent CCE discoveries regarding the chemistry of dihydroxyfumaric acid in aqueous media were studied. The physical organic chemistry of these transformations was extensively studied as well as expanding the small scope of prebiotic substrates to a fully developed chemodivergent methodology to access distinct reaction pathways with minor changes in the conditions of the reactions.

1.5 Structure of Thesis

Chapter 2 will focus on the formal dimer of glyoxylate, dihydroxyfumaric acid (DHF). Both the fundamental stability and chemistry of DHF as well as computational work to explain the reactivity will be discussed. Finally, differences between the dimethyl ester, free acid, and carboxylates of DHF will be explained. A novel deoxalation reactivity of DHF is shown with a combination organic/aqueous solvent system with mixed hydroxide bases.

Chapter 3 expands on the chemistry of DHF focused on the decarboxylative reactivity of DHF. A substantial substrate scope and optimization of the reaction conditions is presented. Reaction cycling exhibited to increase the recovered mass of desired product through iterative addition of excess DHF. Financially feasible synthesis of the natural product *C*-veratroylglycol is also shown in a single step from vanillin. A follow up project taking this synthesis to access similar lignan natural products is laid out.

In Chapter 4, the study of glyoxylate a possible nucleoside linker is studied. Extensive attempts to synthesize, through standard organic methods, a glyoxylate linked nucleoside are laid out. Both acid and base mediated methods with a range of differing

glyoxylate analogs are examined as well as O,S and S,S acetals. A pivot toward a possible novel alcohol protecting group is proposed. Protection and deprotection conditions alongside orthogonality of the new protecting group are examined.

Chapter 5 presents a separate attempt to overcome the intransigence of forming glyoxylate-linked nucleosides. The envisioned model has the glyoxylate tethered to the nucleoside through a 4-carbon chain that would cyclize to form a bicyclic system. This could self-polymerize more easily than nucleosides and glyoxylate. The synthesis of the system proved highly difficult with several unexpected roadblocks. The problems and methods to overcome them along with the current state of the project is shown.

CHAPTER 2: STUDY OF DHF AND NOVEL DEOXALATION MECHANISM

This chapter will focus on the formal dimer of glyoxylate, dihydroxyfumaric acid (DHF). Both the fundamental stability and chemistry of DHF as well as computational work to explain the reactivity will be discussed. Finally, differences between the dimethyl ester, free acid, and carboxylates of DHF will be explained. A novel deoxalation reactivity of DHF is shown with a combination organic/aqueous solvent system with mixed hydroxide bases. All experiments within were published in the Journal of Organic Chemistry Ward *et al*. (DOI: 10.1021 /acs.joc.8b01867) with permission from ACS.[15]

2.1 Background/Introduction

The reactivity of dihydroxyfumaratic acid (DHF) has recently attracted interest in both the context of prebiotic chemistry and synthetic methodology. It has been primarily studied in literature as a reductant. Oxidation/Reduction of the ene-diol to di-oxosuccinic acid or tartaric acid occurs readily and has been observed using different oxidative or reductive conditions.[16,17] Because of its inherent propensity toward oxidation, DHF has been used as an additive in wine preparation as an anti-oxidant.[18] Ene-diols have also been utilized to form substituted methanol ligands.[19] In the presence of oxygen and base, after oxidation, the *trans* electron withdrawing group can migrate resulting in a trisubstituted methoxide anion. Alongside reduction/oxidation, there have been examples where the unique structure, a central alkene substituted at both ends by a hydroxyl and carboxylic acid, allows for interesting bond forming reactivities. This arrangement results in two possible types of carbon-carbon bond forming reactivity: through the unsaturated carboxylic acid utilizing electrophilic reaction pathways or through the ene-diol in nucleophilic pathways (Figure 7). The current literature gives examples of both types.

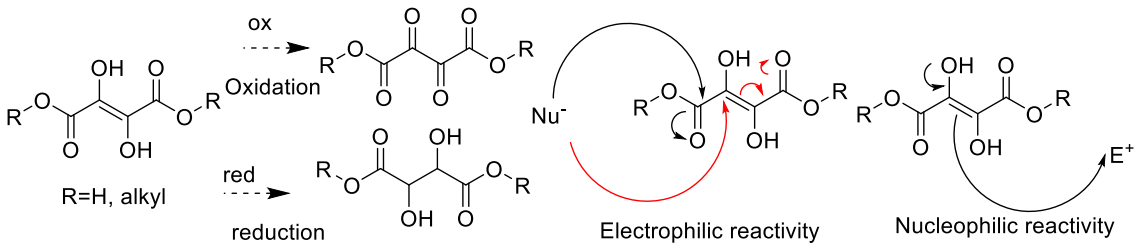


Figure 7 DHF Electrophilic and Nucleophilic Reactivity

Until recently, aside from oxidation/reduction of the ene-diol moiety, the only examples for bond forming reactions involved electrophilic addition of nucleophiles to the unsaturated carboxylic acid motif of DHF.[20,21,22] Acetylation of the hydroxyl groups was often used to facilitate attack of a nucleophile onto the unsaturated ester portion. Aryl amine or aniline attack, followed by ring closure through Friedel-Craft addition to the aryl group to form carboxylated quinoline and other nitrogen containing heterocycle type compounds.[23] In all cases the carboxylic acid of DHF was capped as an alkyl ester.

The lack of any examples of nucleophilic DHF activity was first changed by the CCE. Because of the hypothesized connection between glyoxylate and DHF presented by Eschenmoser, Krishnamurthy *et al.* began to investigate possible reactivity between these two molecules (Figure 8).[24] While under acidic conditions no reactivity was observed, when the lithium or cesium salt of DHF is reacted with glyoxylate clean conversion to dihydroxyacetone and pentulosonic acid was observed.[24] The intermediates of the decarboxylative aldol reaction were all confirmed and observed through NMR reaction monitoring. After initial aldol addition forming the six carbon tricarboxylate, two iterative decarboxylations follow to lead toward the dihydroxyacetone. The surprising pentulosonic acid occurs via a second addition of glyoxylate. This was confirmed by performing the same reaction with ^{13}C labeled glyoxylate allowing for the carbons to be followed and

determining where each originated from. Other prebiotically plausible aldehydes: formaldehyde, glycolaldehyde, and glyceraldehyde were also amenable toward this chemistry. While the ability to form these collections of sugars and sugar acids in a prebiotic fashion is interesting in the origin of life field unfortunately there was no way to utilize this new chemistry to access synthetically useful transformations.

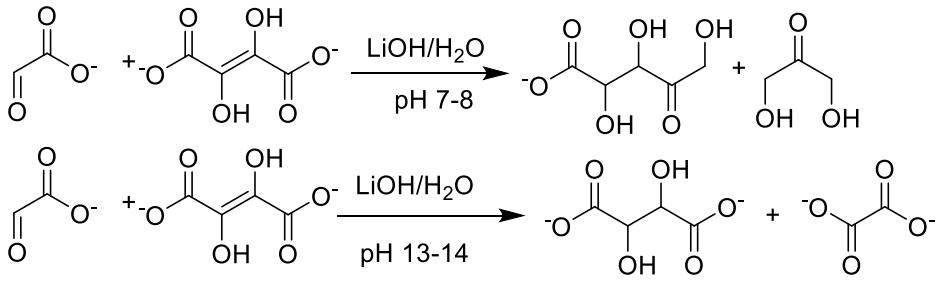


Figure 8 Chemodivergent Reactivity of DHF and Glyoxylate[24-26]

A follow-up investigation by Butch *et al.*[25] expanded on the chemistry of DHF in basic aqueous media. Initial thrust of the investigation was looking for ways to generate DHF *in situ* and perform the reaction with glyoxylate without having to start with DHF. While testing different conditions, it was discovered that when DHF reacted with glyoxylate in a highly basic environment (pH 13-14) a distinct product distribution was observed. Tartrate and oxalate were formed instead of sugar acids. While it could be imagined that these products are formed through a redox process between DHF and glyoxylate carbon labeling studies of this novel reaction determined that there is formation of new carbon-carbon bonds. The initial aldol addition of DHF onto glyoxylate is followed, contrary to the pH 7-8 conditions, by a novel deoxalation fragmentation. Protonation of the resulting carbanion yields the tartrate product cleanly with the oxalate as the only biproduct. This reaction is a formal aldol addition of glycolic acid without the need to protect the acid. Production of tartrate is particularly interesting on a prebiotic

level as it is a key intermediate in the citric acid cycle used by life to generate cellular energy. Liotta and Krishnamurthy took these two reactions and summarized the competitive nature of the chemistry in a physical organic paper but focused on the biomimetic properties of the reactions. From this the chemodivergent capabilities of DHF as a nucleophile was clarified but again there was an issue with determining how this could be used and expanded beyond glyoxylate.[26]

Only one previous study has been published attempting to expand either of the two nucleophilic DHF reactivities. Mahrwald *et al*. in 2016 investigated the decarboxylation of DHF with aryl aldehydes (Figure 9).[27] By applied conditions published by Sagi *et al.* lithium and cesium salts were used in a mixed dioxane: H_2O solvent system. In the vast majority of cases the homoaryl propanone was observed in low to fair yields. Isomerization to the aryl propanone was achieved only by addition of 50 mol % of brucine to the reaction. This study suffered from some problems that led to the belief that it could be improved on alongside accessing the deoxalative pathway in a synthetically useful method. The products in most cases were isolated in fair yield but were not clean isolations. There were significant impurities in the products. This suggested that something is making this reaction significantly messier than the glyoxylate reactions as those were clean conversions. Secondly, the isolation of homoaryl propanones instead of aryl propanones allows for a change in conditions to achieve a different structural motif. The deoxalative pathway had not been achieved to this point.

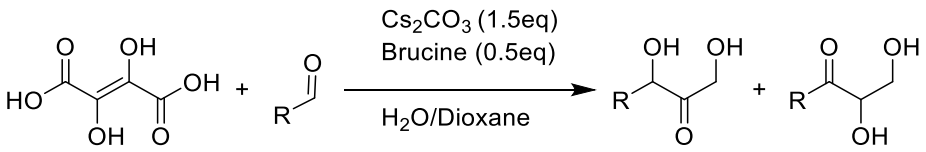


Figure 9 Mahrwald's Decarboxylation Conditions[27]

At this junction, while the synthetic possibilities of the decarboxylative aldol pathway has been demonstrated by Mahrwald *et al.*, the synthetic generalization of the chemodivergence reported by Butch *et al.* has not yet been addressed.[27] In this Chapter, we discuss our successful efforts toward base-promoted chemodivergence in the reactions of (hetero)aryl aldehydes with DHF in organic solvents by the careful choice of base and the synthetic utility of these transformations (Figure 10). Also, we analyze how differences in DHF derivatives result in dramatic physical and chemical differences. From solubility to self-condensation and aerobic oxidation, minor differences result in significant changes.

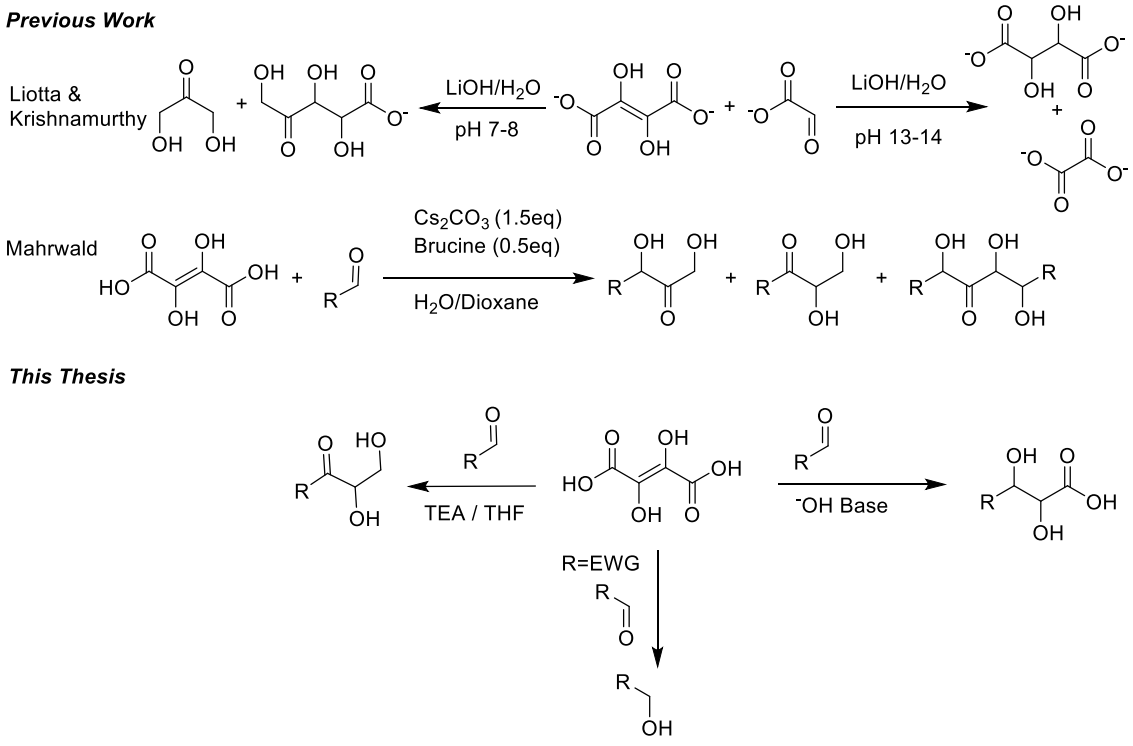


Figure 10 Summary of DHF Chemodivergent Methodology[24-28]

2.2 Computational Analysis of DHF Analogs

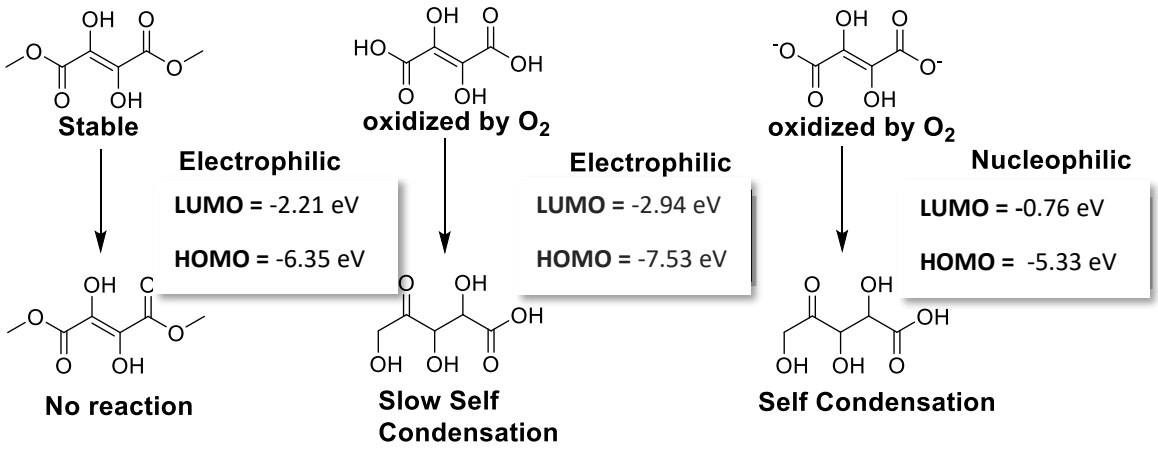


Figure 11 Computational Analysis of DHF and Analogs

From the current literature, there is evidence that the nature of the carboxylic acid has a profound effect on the reactivity of DHF toward either nucleophiles or electrophiles. In all cases of electrophilic reactivity, the carboxylic acid was capped as an alkyl ester while when reacting in a nucleophilic fashion the acids were always free and a base was added to the mixture likely resulting in the carboxylate as the reactive species of DHF. Even with this clear trend in the literature there has been no focused study on why seemingly minor changes to the carboxylic acid moiety has a profound effect on the reactivity.

Computational studies of DHF shed some light on this trend as well as other interesting properties of the molecule (Figure 11). As expected, changes on the carboxylic acid drastically effects the HOMO and LUMO energies. The methyl ester of DHF (DiMeDHF) and DHF have similar energies, -6.35 eV to -2.21 eV and -7.53 eV to -2.94 eV. Deprotonation of DHF to the dicarboxylate shifts these values up to -5.33 eV to -0.76 eV. There is also more partial negative charge on the central carbons of the dicarboxylate

when compared to DiMeDHF and DHF. Both of these results support the hypothesis that the formation of the dicarboxylate is necessary to facilitate any type of nucleophilic reaction by DHF. Another discovery explains why DHF is so soluble in organic solvents while the dicarboxylate and DiMeDHF are not. In the free acid form the molecule adopts a very ordered intramolecular hydrogen bond arrangement which hides the multiple highly polar functional groups.

2.3 Stability and Self-reactivity of DHF and Derivatives

The importance of the carboxylic acid moiety is also evident in the relative stability of each derivative toward self-reaction and atmospheric oxygen. As shown in Figure 7, DiMeDHF is bench stable under air for months with no degradation or self-condensation observed by NMR spectroscopy in the solid state or in solution. It is also surprisingly insoluble in common organic solvents with only DCM dissolving it at room temperature at low (<0.05M) concentration. Refluxing is required to dissolve into other systems. Upon cooling DiMeDHF can be recollected quantitatively. The DHF free acid is oxidized by oxygen but it still can be stored in a refrigerator without rigorous degassing of the container. In solution, DHF will slowly self-react to form the shown sugar acid. DHF is much more soluble than DiMeDHF in organic solvents which is odd as in general esters are more soluble. Finally, the dicarboxylate will be quickly oxidized by oxygen so it needs to be stored in a freezer and ideally under a nitrogen balloon to retain its purity for any length of time. The self-condensation in water has been shown by Liotta[26] to proceed cleanly in only a few hours.

From the current literature, there is evidence that deprotonation of DHF to provide its dicarboxylate (DHF^{2-}) is critical to unveiling its nucleophilicity. Deprotonation

effectively minimizes the orbital overlap between the delocalized carboxylate anions and the electron-rich ene-diol portion of the molecule. To the best of our knowledge, in cases where DHF behaves as an electrophile, the carboxylic acids of DHF existed as alkyl esters.[21-23] In contrast, when reacting as a nucleophile, the carboxylic acid groups of DHF were always ionized using basic media.[26-28] Even with this clear trend in the literature there has been no focused study on why seemingly minor changes to the carboxylic acid moieties of DHF have a profound effect on its reactivity. The relative stabilities of the DHF derivatives, especially toward reaction with atmospheric oxygen (to form di-oxosuccinic acid) and self-condensation (via the putative keto form of DHF^{2-} to form sugar acid **5**, Figure 12) also seem to be affected by state of ionization of DHF versus its ester derivatives.

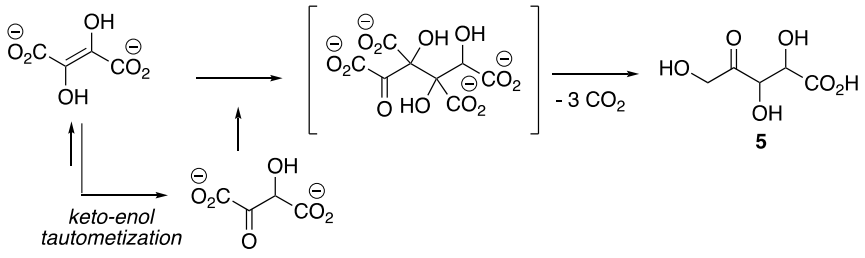


Figure 12 Self-Condensation of DHF^{2-} in H_2O

It is also surprisingly insoluble in most common organic solvents dissolving giving rise to dilute solutions in dichloromethane or chloroform at room temperature. Heating at reflux is required to dissolve DiMeDHF in THF or 1,4-dioxane. Upon cooling, DiMeDHF can be recovered quantitatively. Treating DiMeDHF with an electrophile, such as benzaldehyde or 4-nitrobenzaldehyde, in chloroform-*d* at room temperature resulted in no observed reaction (Figure 13). Conducting the reaction in THF at reflux or with added base (i.e., NEt_3) also failed to provide any observable reaction by crude NMR. With H_2SO_4 as

the aldehyde activator, only degradation of the starting materials was observed. This suggests that the ene-diol moiety in ester **11** is unreactive as a nucleophile towards reactive electrophiles such as aryl aldehydes.

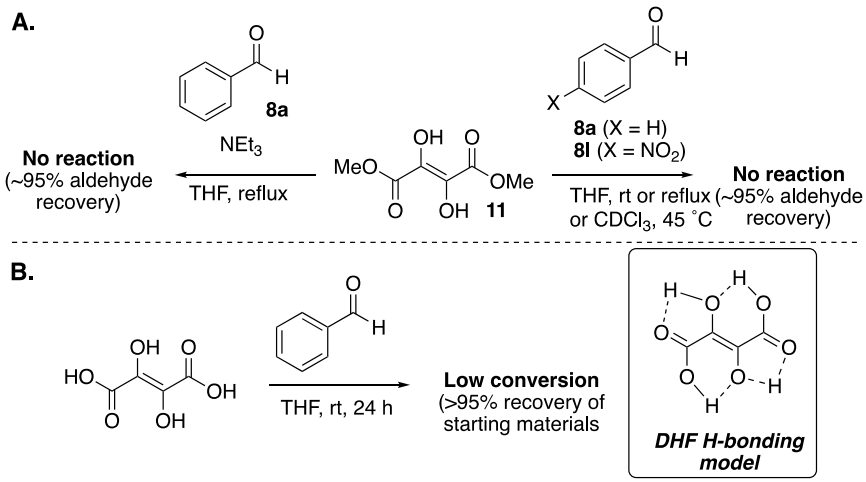


Figure 13 Probing DiMeDHF (A) vs DHF Free Acid (B) Nucleophilic Reactivity

When compared to DiMeDHF, DHF (as the free acid) is oxidized by oxygen but it still can be stored in a refrigerator without rigorous degassing of the container. DHF is much more soluble than DiMeDHF in organic solvents which is odd as, in general, esters are more soluble. The differences in solubility between DiMeDHF and DHF can be rationalized by the fact that in DHF, the molecule is expected to adopt a very ordered intramolecular hydrogen bond arrangement which, ultimately, hides the multiple highly polar functional groups and increases organic solubility. The reactivity of DHF as the free acid in organic solvents has not been studied. To probe this, we performed a control reaction in which DHF (free acid) was stirred in THF and the solution monitored daily by ^{1}H NMR spectroscopy (Figure 13). After 3 days, only ~10% of DHF was consumed forming a trace amount of pentulosonic acid via self-condensation. As further proof of DHF acid's poor nucleophilic behavior, extremely low conversion (<5%) was observed by

^{1}H NMR when DHF (free acid) was stirred with an electrophile (i.e., benzaldehyde) in THF after 24h.

Finally, in contrast, the dicarboxylate can be rapidly oxidized by O_2 so it needs to be stored in a freezer and ideally under a nitrogen balloon to retain its purity for any length of time. The self-condensation of DHF^{2-} in water has been shown by Sagi et. al.[28] to proceed cleanly to sugar acid **5** in only a few hours.

2.4 Optimization the Reaction of DHF with Benzaldehyde and Hydroxide Bases- The Deoxalation Pathway.

With this understanding of the nucleophilic behavior of the dicarboxylate form of DHF, we sought to expand the scope of the work by Sagi et al.[28] and Butch et al.[26] by exploring the reactivity of aryl and heteroaryl aldehydes toward the observed chemodivergence. Benzaldehyde was selected as the substrate for optimization and various bases and solvent systems (e.g., organic, aqueous, and mixed)) were screened to first determine conditions selective for the deoxalation pathway. The results are summarized in Table 1. It was previously shown by Sagi et al.[24] and Butch et al.[26] that two hydroxide molecules (one as a nucleophile, one as a base) are necessary to promote the deoxalation pathway (Figure 14).[25]

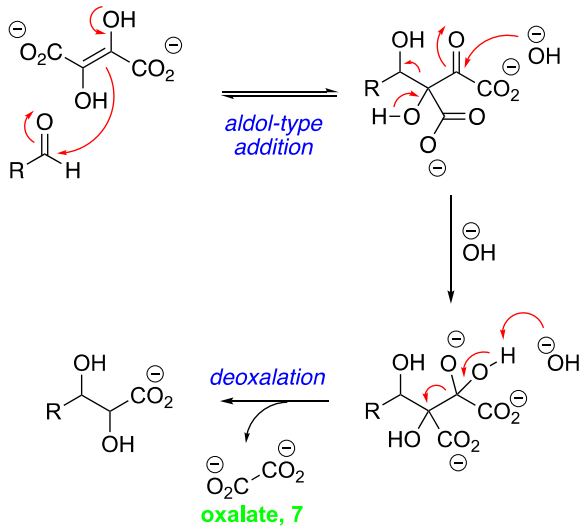
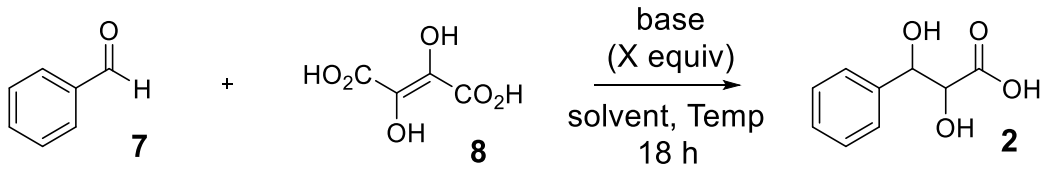


Figure 14 Deoxalation Pathway and the Importance of Hydroxide

When 4 equivalents (2 equiv to form dicarboxylate and 2 equiv to promote deoxalation) of either TBAH, NaOH, or LiOH were included in the THF reaction, only Cannizzaro reaction products (e.g., benzoic acid, benzyl alcohol, etc.) were observed (Table 1, entries 1-3). Addition of 1 equivalent of 15-crown-5 (to activate the hydroxide) with NaOH in THF gave the desired deoxalation product **9a** in 56% yield as a diastereomeric mixture of the sodium carboxylate complexed to the crown ether (entry 4). Reducing the amount of 15-crown-5 to 0.5 equiv resulted in a severe drop in yield (23%, entry 5). Using of 2 equiv of NaH (to form the DHF dicarboxylate) and 2 equiv of NaOH with 1 equiv of the crown ether improved the yield of the deoxalation product **9a** to 75% yield (entry 6). Unfortunately, efforts to remove the 15-crown-5 by acidification or ion exchange either resulted in degradation or substantial loss of material. Moreover, the presence of the crown ether made characterization using NMR extremely difficult due to overlapping aliphatic signals with the product. Given the difficulty in purification of the product and the requirement of a full equivalent of crown ether, we abandoned this approach and looked for other conditions that would facilitate the deoxalation reaction

without the necessity of crown ether.

Table 1 Deoxalation Conditions Screening



Entry	Base (equiv)	Solvent (Temp)	Yield (%)
1	TEA (4)	THF	72%[d]
2	TEA:NaOH (3:1)	THF (65)	58%[d]
3	NaOH (4)	THF (rt)	X
4	LiOH (4)	THF (rt)	X
5	TBAH (4)	THF (rt)	X
6[a]	NaOH (1eq 15-c-5)	THF (rt)	56%
7[a]	NaOH (0.5eq 15-c-5)	THF (rt)	23%
8[a]	NaH:NaOH (1eq 15-c-5)	THF (rt)	75%
9	NaOH	THF:H_2O (1:1)	X
10	NaOH	H_2O	X
11[b]	NaOH:LiOH (4:2)	H_2O	X
12[b,c]	NaOH:LiOH (4:2)	THF:H_2O (1:47)	72%
13	NaOH:LiOH (4:2)	THF:H_2O (1:3.5)	25%
14	NaOH:LiOH (4:2)	THF:H_2O (1:1)	25%
15	NaOH (4)	glyme	degrade
16	NaOH (4) – TBACl (1)	THF (rt)	degrade
17	NaOMe (4)	THF (rt)	degrade
18[a]	nBuLi:NaOH (2:2) – 15-c-5	THF (-78-rt)	43
19	NaH:LiOH (2:2) -12-c-4	THF (rt)	X
20	LiOH – 12-c-4	THF (rt)	Degrade
21	NaH:KOH (2:2) – 18-c-6	THF (rt)	X
22	KOH (4) – 18-c-6	THF (rt)	degrade
23	NaH:$Ba(OH)_2$ – 18-c-6	THF (rt)	X
24	$Ba(OH)_2$ (4) – 18-c-6	THF (rt)	X
25	CsOH – 18-c-6	THF (rt)	X

[a] product isolated as crown ether complex. Attempts to remove it all failed.
[b] slow addition of LiOH and DHF in water.
[c] Aldehyde added in THF (0.15mL/ 15M)
[d] decarboxylation product
[e] qNMR yield with dimethyl sulfone as standard
X=> Cannizzaro reaction products observed exclusively.

Given this issue, we went back to the drawing board and decided to directly adapt the published aqueous method from Sagi et al.[24] and Butch et al.[25] NaOH (6 equivalents) in H_2O or in a 1:1 THF-H_2O mixture only provided Cannizzaro reaction products (entries 7 and 8). Previous work had indicated that a combination of both LiOH (2 equiv) and NaOH (4 equiv) afforded better results as the DHF dilithium salt is much more soluble in water than the sodium salt. Unfortunately, initial combination of these bases either in H_2O or in a 1:1 THF-H_2O mixture continued to produce Cannizzaro products (entries 9 and 10). Interestingly, employing a lower THF to H_2O ratio and changing the order of addition was key in the development of a successful process. Benzaldehyde dissolved in THF (2 mL) was added to a solution of NaOH in H_2O (5 mL) followed by slow addition of DHF and LiOH in H_2O (2 mL) to give a 1:3.5 THF-H_2O mixture. Using this sequence, deoxalation product **9a** was observed (entry 11). Since the product could not be extracted into the organic phase, the reaction mixture was treated with Amberlyst 15 resin to acidify the solution and remove the sodium and lithium cations and the organic soluble byproducts were removed by extraction. Upon concentration of the aqueous phase, a 25% yield of deoxalation product **9a** was observed by quantitative ^{1}H NMR along with a collection of other unidentified peaks. Reducing the amount of THF used to dissolve the benzaldehyde to ~0.23 mL resulted in a 1:30 THF-H_2O ratio and gave a 45% ^{1}H NMR yield (entry 12). In the end, the addition of a minimal amount of THF (0.15 mL) to dissolve benzaldehyde (providing a 1:47 THF-H_2O solution) proved to be the best conditions, with a 72% ^{1}H NMR yield observed for deoxalation the product **9a** (entry 13).

2.5 Deconvoluting Deoxalation from DHF Self-Condensation Pathways

We hypothesized that the undesired peaks in the deoxalation reaction arose from DHF self-condensation. To test that hypothesis, we exposed DHF to the deoxalation reaction conditions in the absence of benzaldehyde (Figure 15). Through spiking studies as well as comparison to literature precedent[25] we determined that the signal at 174.3 ppm is glycolic acid (**13**), the pair of peaks at 173.3 and 172.8 ppm are the two diastereomers (D/L and *meso*) of tartaric acid (**6**), and the peak at 170.8 ppm is tartronic acid (**12**). 2-D NMR experiments and DEPT further confirm these identifications. Comparing the control reaction against the same reaction with 3 equiv of benzaldehyde, the signals at 174.1 and 174.0 ppm represent the diastereomers of the deoxalation product while the same peaks from DHF self-condensation are also observed (Figure 5B). A signal for oxalic acid can also be observed at 162.2 ppm.

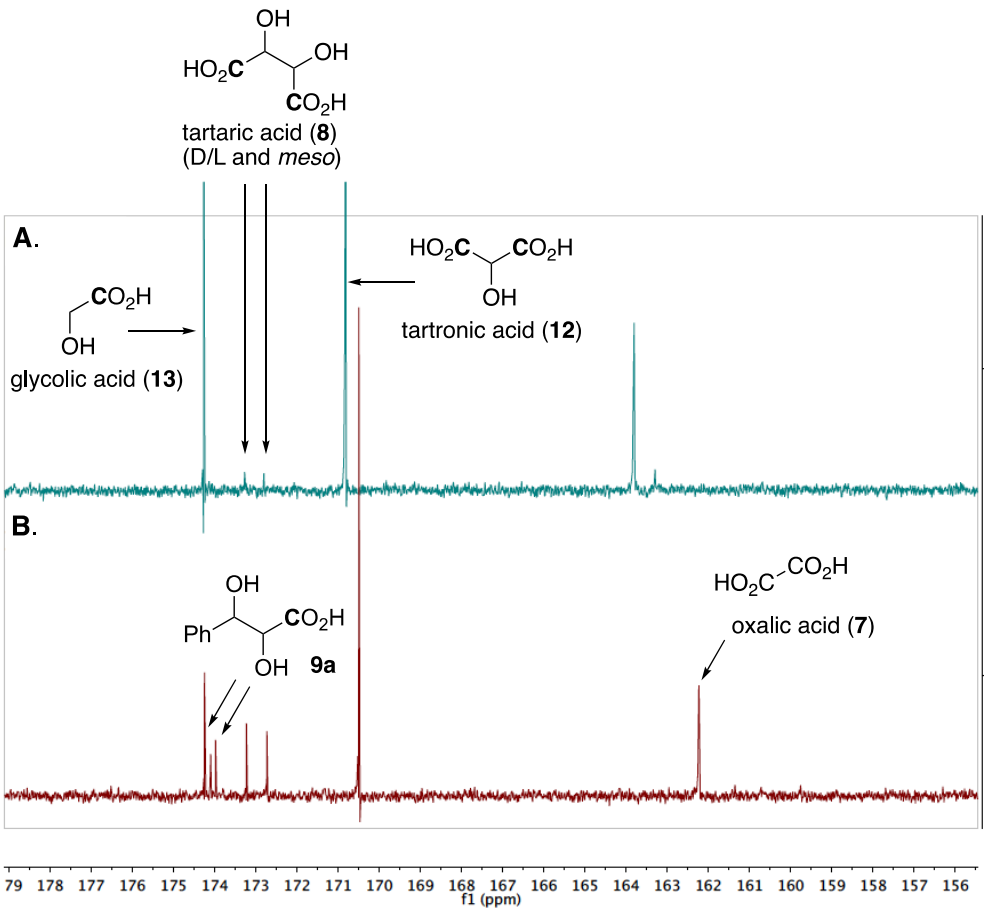


Figure 15 Crude ^{13}C NMR (DMSO-d_6) of Reactions of (A) DHF with NaOH:LiOH (4:2) in THF:H_2O (1:3.5) and (B) with 3 eq of Benzaldehyde added after Acidification

We envision a range of different pathways that DHF can undergo to form the observed byproducts under strong basic conditions (Figure 16). These pathways are distinct from the previously published self-reactivity of DHF under slightly basic conditions (pH 8). A single DHF molecule can fragment to form glycolate (**13**) and glyoxylate (**2**). Glyoxylate is a highly reactive species that has already been shown to react with DHF to form tartrate (**6**) through a deoxalative mechanism.[24] Dimerization of DHF forms the tetra-carboxy intermediate **I**, which undergoes decarboxylation to form **II**. **II** can also tautomerize to **III** then proceed through a deoxalation-like cleavage mechanism

to release tartronate (**12**) and tartrate. Tartronate can also decarboxylate to produce glycolate. The three observed products are the only non-volatile, stable products from the self-reactivity of DHF at high pH after acidification. It is important to mention that the observed peak ratios do not accurately represent how much condensation products are formed. Based on the proposed mechanism, tartrate should be generated in a greater amount than tartronate. However, the NMR shows a much larger amount of tartronic acid than tartaric acid. This discrepancy is an artifact of the workup procedure. Some tartrate is extracted into the organic phase and some undergoes degradation following the acidic workup.

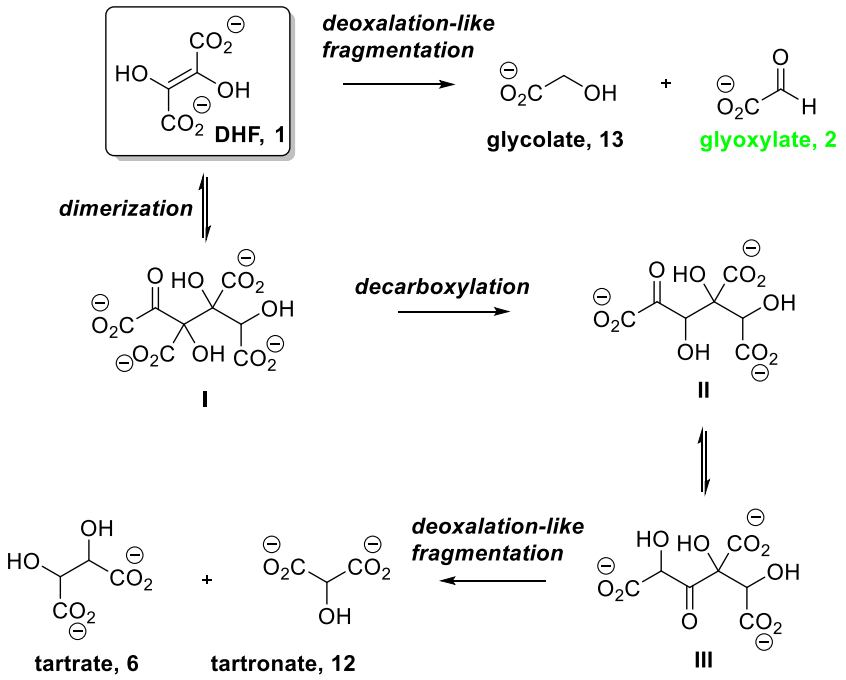
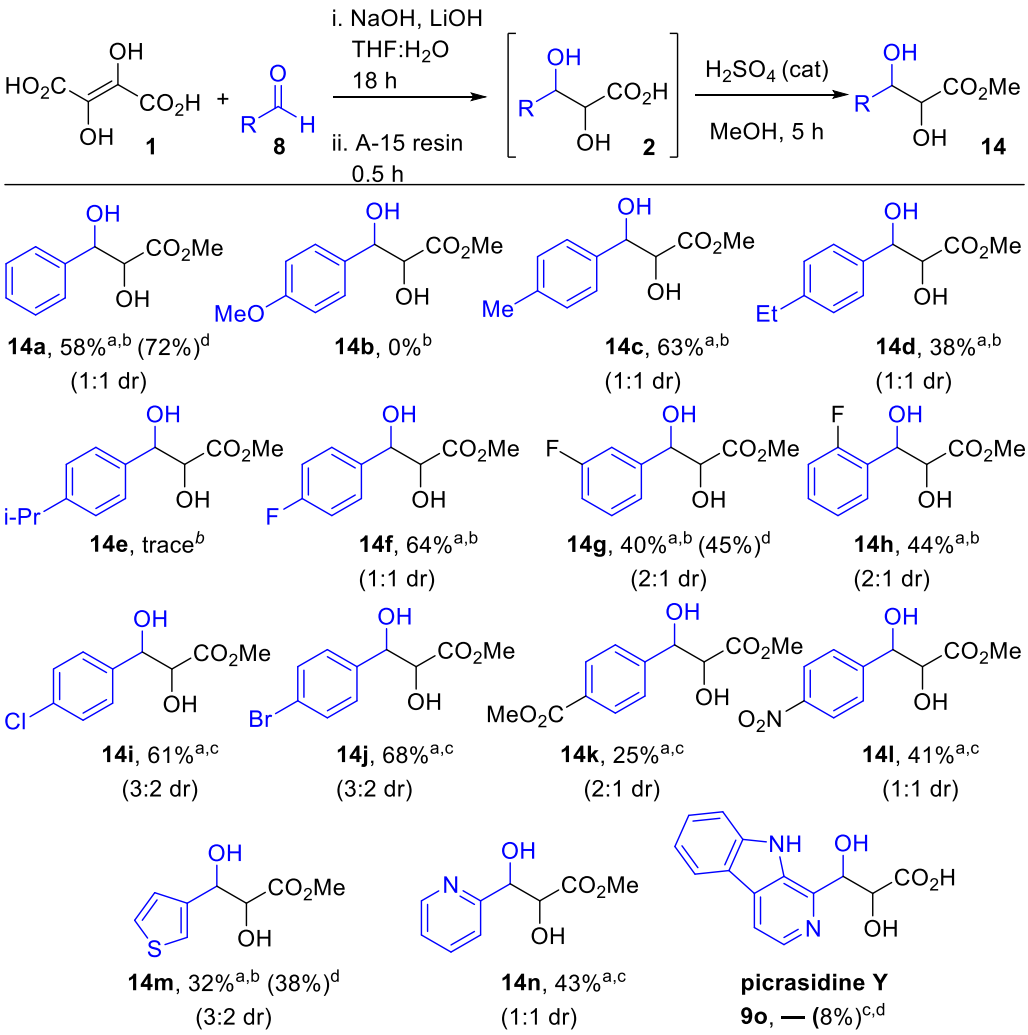


Figure 16 Proposed Mechanism for the Origin of Tartronic Acid (12), Tartaric Acid (6) and Glycolic Acid (13)

2.6 Examination of Substrate Scope of Deoxalation Reaction.

With working conditions for the deoxalation reaction in place, we next examined the scope and limitations of employing various aryl and heteroaryl aldehydes (Figure 17). Instead of relying on quantitative NMR, we decided to derivatize the products to the corresponding methyl esters for easy isolation via column chromatography. Heating the crude mixture with catalytic H_2SO_4 in MeOH readily afforded esterification products in greater than ~80% yield. For instance, the deoxalation product from benzaldehyde was converted to its methyl ester in 81% yield. This gave an overall yield of 58% for the two steps upon isolation. The ester **14a** was isolated as a 1:1 mixture of diastereomers.



[a] Isolated yield of ester **14** (over two steps)
[b] THF:H_2O (1:47)
[c] THF:H_2O (1.3.5)
[d] qNMR yield of acid **9**

Figure 17 Hydroxide-Mediated Cascade Aldol-Deoxalation Reactions

We then probed electronic effects on the reaction by looking at 4-substituted benzaldehydes. The reaction with 4-anisaldehyde failed to provide any desired deoxalation product, whereas 63% yield of dihydroxyester **14c** was obtained with 4-tolualdehyde (**8c**). In contrast to tolualdehyde, the 4-ethylbenzaldehyde **8d** gave 38% yield of **14d** whereas only trace product was observed with 4-isopropylbenzaldehyde **8e**. 4-Fluorobenzaldehyde (**8e)** was similarly compatible with the reaction sequence forming dihydroxy ester **14e** in

64% yield. Both 3-fluoro- and 2-fluorobenzaldehydes (**8f** and **8g**) similarly gave their corresponding methyl esters **14f** and **14g** in 40% and 44% yield, respectively. 4-Chloro- and 4-bromobenzaldehydes (**8h** and **8i**) are solids and were not readily solubilized in the amount of THF (0.15 mL) used in the 1:47 THF-H_2O mixture. To ensure solubility, 2 mL of THF was used to dissolve the solids before addition to the aqueous DHF/base solution (resulting in a 1:3.5 THF-H_2O mixture). In this solvent system, the respective chloro and bromo ester products **14h** and **14i** were obtained in 63% and 68% yield. Stronger electron-withdrawing groups on the phenyl ring, such as 4-CO_2Me and 4-NO_2, were also amenable to the reaction, albeit with reduced yields. 4-CO_2Me-benzaldehyde (**8j)** only gave 25% yield of the ester product **14j** while 41% yield of ester **14k** was obtained with the 4-NO_2-benzaldehyde (**8k)**. In both cases, increased amounts of Cannizzaro reaction products were observed.

Several heteroaryl aldehydes were also examined under the reaction conditions. 3-Thiophencarboxaldehyde **8l** gave 38% qNMR yield of **9l** and a 32% yield of ester **14l** over the two steps. 2-Formylpyridine (**8m**) performed similarly and gave 43% yield of ester **14m**. Finally, 1-formyl β-carboline (**8n**) was subjected to the reaction conditions to form the natural product, Picrasidine Y[29] (**9n**). **9n** was formed in 8% yield by qNMR along with several undesired side products (including Cannizzaro products). Protection of the carboline would most likely improve the product yield given the strong basic conditions and the acidic carboline proton. Picrasidine Y has been previously synthesized in 7 steps[29] using tartaric acid. Despite the low yield, this synthesis thus represents a one-step approach to Picrasidine Y which could offer a rapid opportunity for compound library development by employing substituted 1-formyl-β-carbolines.

2.7 Conclusion

Throughout this work, the general understanding of how DHF reacts under basic conditions. This adds a major new section of DHF chemistry as previously it was seen primarily as an electrophilic species. The competing moieties, unsaturated ester and ene-diol, dominate the reactivity. When the conjugation between the carboxylic acid and alkene is broken through increasing the electron density in the carboxylic acid, i.e. deprotonated, allowed for nucleophilic reactivity to dominate. Both experimental as well as computational results support the hypothesis that deprotonation is key to achieve reactivity. With a combination of hydroxide bases, the novel prebiotic deoxalation discovered in the CCE was achieved with a range of different aryl and heteroaryl aldehydes. This formal aldol addition of glycolic acid to aldehydes without protecting groups expands the toolbox of methods to form dihydroxy carboxylic acids. While developing this method, a study of the self-fragmentation of DHF was undertaken to attempt to deconvolute the crude reaction mixture. Under these highly basic conditions, DHF will degrade to glycolate, tartrate, and tartronate. All of these results will assist in bringing DHF into the organic synthetic realm as a useful substrate for natural product synthesis. This is an excellent example of how prebiotic chemistry can be taken from the strictly theoretical origin of life realm and be useful to the rest of the chemistry community.

CHAPTER 3: EXPANSION OF DHF DECARBOXYLATION METHOD

This chapter expands on the chemistry of DHF focused on the decarboxylative reactivity of DHF. A substantial substrate scope and optimization of the reaction conditions is presented. Reaction cycling exhibited to increase the recovered mass of desired product through iterative addition of excess DHF. Financially feasible synthesis of the natural product *C*-veratroylglycol is also shown in a single step from vanillin. A follow up project taking this synthesis to access similar lignan natural products is laid out. All experiments within were published in the Journal of Organic Chemistry Ward *et al*. (DOI: 10.1021 /acs.joc.8b01867) with permission from ACS.[15]

3.1 Introduction

2,3-Dihydroxypropiophenones (**1**) represent a class of highly oxidized alkyl chains that have been garnered the attention of synthetic chemists for many years.[29] They represent a diverse set of compounds that include both pharmaceutically-relevant lignin and non-lignin natural products and synthetically-derived compounds (Figure 18). For instance, *C*-veratroylglycol (**2**) has demonstrated modest antiproliferative activity against human colon cancer cells[30] and moderate inhibitory activity against COX-2[31] and is found in different varieties of plant extracts. Other 2,3-dihydroxypropiophenones like prunustosanan AIII (**3**)[32] and its cogeners are unique to the *Rosaceae* plant family. 2,3-Dihydroxypropiophenones are also valuable as precursors to access the corresponding triols following ketone reduction.[33] Similarly, other derivatives that have been isolated are the 2-aryloxy-3-hydroxypropiophenones, which include wikstroemone (**4**)[34] and icariol A_1 (**5**).[35] Besides the parent compounds, the corresponding heteroaryl analogues are also

naturally-occurring. In a representative example, oxopropaline D (**6**) is part of an interesting family of cytocidal 9*H*-pyrido[3,4-*b*] indolyl 2,3-dihydroxypropionones.[36,37,38]

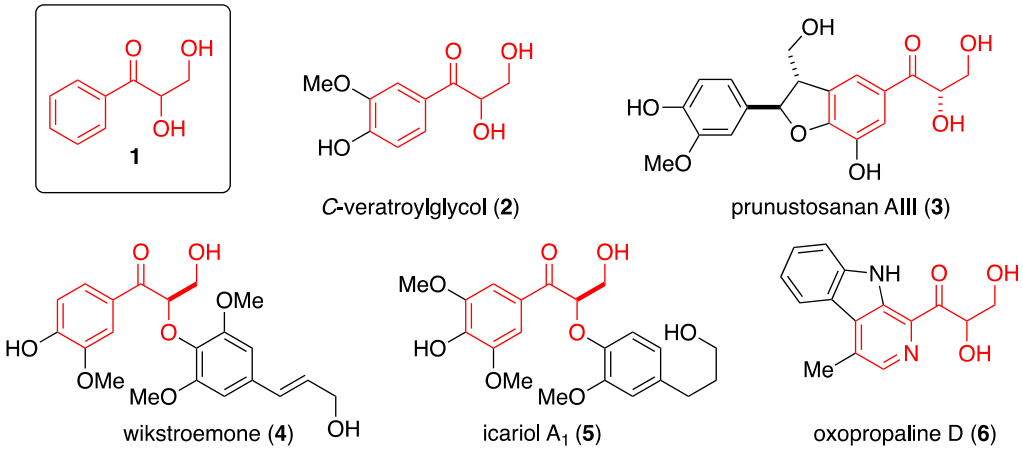


Figure 18 Representative Naturally-occurring 1-(Hetero)aryl Dihydroxypropionones and the Derivatives

Despite the prevalence of (hetero)aryl 2,3-dihydroxylpropionones in nature, only a small subset has been examined for biological activity due to the low abundance of the individually isolated compounds. Consequently, the development of synthetic approaches that can rapidly access the structural diversity in this compound class has become a worthwhile endeavor.

One of the most commonly employed approaches toward aryl 2,3-dihydroxypropionones involves either the preparation of the α,β-unsaturated aryl ketones followed by dihydroxylation or preparation of the aryl vinyl carbinol followed by dihydroxylation and subsequent oxidation of the benzylic OH (Figure 19).[39] This approach is limited due to the overall number of steps and reduced yields involved in preparation of the enones (or carbinols) and the subsequent dihydroxylations. Moreover, toxic osmium salts are needed for the dihydroxylations and pyrophoric reagents are used to prepare the carbinols or enones. In an effort to consolidate the steps, Fernandes and coworkers

developed a tandem benzylic oxidation/dihydroxylation of the aryl vinyl carbinols.[40] The resulting 2,3-propanones were formed in 43-58% yield as mixtures with 21-45% yield of the corresponding triols (no benzylic oxidation). For electron-poor aryl rings, no propiophenone products were detected. More recently, a keto-hydroxylation of cinnamyl acetate was reported for the synthesis of 2,3-dihydroxypropiophenone, although no other substrates were examined.[41]

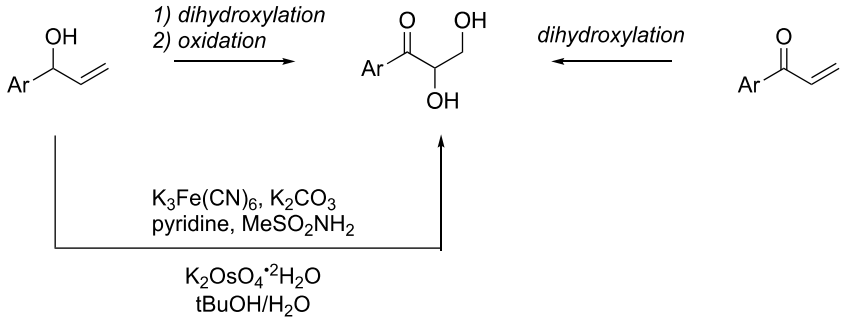
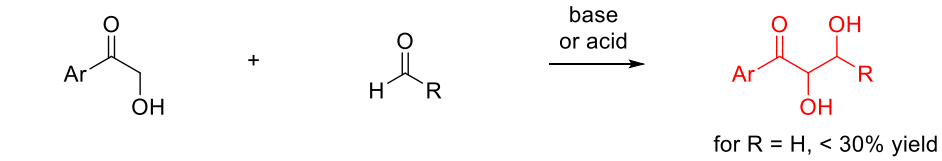


Figure 19 Dihydroxylation Approaches to 2,3-Dihydroxypropiophenones

All of the limitations involving the dihydroxylation sequences have sparked the development of direct aldol-type methods toward 2,3-dihydroxypropiophenones (Figure 20). These include the direct aldol reactions of α-hydroxy aryl ketones with aldehydes in the presence of acids or bases (Figure 20A).[42] While aldol reactions of α-hydroxy aryl ketones are efficient for most aldehydes, the reactions with formaldehyde are notoriously low yielding,[43] with the formation of multiple side products that severely retards purification. An alternative aldol approach that offers promising access to 2,3-dihydroxypropiophenones is the reaction of dihydroxyfumaric acid (DHF, **8**) with aldehydes. Inspired by the work of Krishnamurthy[24] and Liotta[25,26] for the pH-mediated, decarboxylative aldol-type reactions of DHF with glyoxylate and glycolaldehyde, Mahrwald[27] reported the reactions of various alkyl and aryl aldehydes with DHF (Figure

20B). In the case of aryl aldehydes, 2,3-dihydroxypropiophenones **1** were observed with 50 mol % brucine and Cs_2CO_3. Only three examples were shown and the yields were fairly low (13-38%). Interestingly, without brucine, propiophenones were observed sparingly with the isomeric 2-aryl dihydroxyacetones obtained instead as the major product.

A. Aldol Reaction with α-Hydroxy Acetophenones



B. Decarboxylative Aldol Reaction Cascade with Dihydroxfumaric Acid

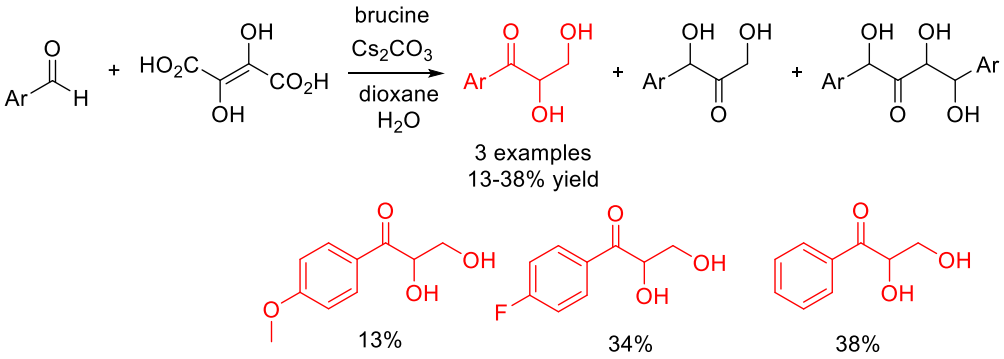


Figure 20 Aldol-type Approaches to 2,3-Dihydroxy Propiophenones

The transformation represents a formal C-H alkylation in which the aldehyde hydrogen is replaced by an ethylene glycol moiety. Intrigued by a potential expansion and direct synthetic application of the work by Krishnamurthy and Liotta and in line with our general interest in C-H functionalization[44], we sought to improve the reaction efficiency and overall chemo- and regioselectivity. Herein, we report our efforts in developing a triethylamine-mediated sequential decarboxylative aldol-type reaction of aryl aldehydes and DHF (**8**) to form both 2,3-dihydroxypropiophenones **1** and heteroaryl 2,3-dihydropropionones **10** (Figure 21).

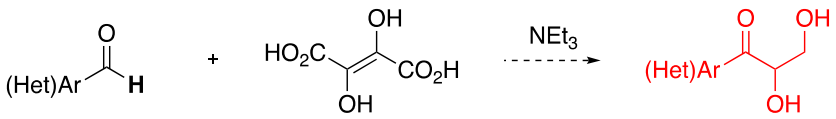


Figure 21 Decarboxylative Aldol-type Reactions of Aryl Aldehydes with DHF mediated by TEA

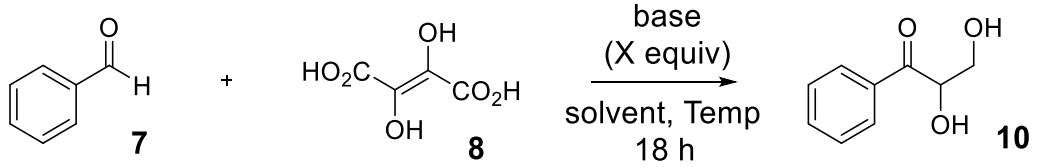
3.2 Optimization of the Reaction of DHF with Benzaldehyde and Tertiary Amine Bases- The Decarboxylation Pathway.

While searching for a viable protocol for the deoxalation reaction, we simultaneously probed for conditions to selectively promote the decarboxylation reaction (Table 2). Given that trace decarboxylation products were detected in the reaction of DHF and benzaldehyde with no added base in THF at room temperature (entry 1), we started by increasing the reaction temperature. Upon heating the reaction at reflux, 2,3-dihydroxypropionone **10a** was obtained in 15% yield as the only decarboxylation product (entry 2). This observation runs counter to what was expected based on Mahrwald's decarboxylation work.[27] In that report for aryl aldehydes, the isomeric aryl-substituted dihydroxyacetones or diaryl trihydroxybutanones were predominantly formed. Only three examples of aryl 2,3-dihydroxypropionone formation were shown. To effect the transformation, brucine (50 mol %) and Cs_2CO_3 (1.5 equivalents) were employed, but the yields were low (13-38% yield) in each case. In contrast, our reaction provides selective mono-aldol additions (despite using excess aldehyde) and formation of the dihydroxypropionones. It is also important to note that the transformation represents a formal C(sp^2)-H alkylation of the aromatic aldehyde without involving any transition metal-based chemistry.

Next, bases were screened to facilitate the decarboxylation reaction at 65 ˚C. The use of hydroxides, alkoxides, or carbonate bases resulted in Cannizzaro reaction (entries 3-

5). Next, tertiary amine bases were added. With Hünig's base (iPr_2NEt, 4 equiv), **10a** was obtained in 25% yield (entry 6). While no product formation was detected with DBU (entry 7), NEt_3 afforded **10a** in 68% yield (entry 8). Increasing the amount of NEt_3 to 6 equivalents resulted in a 62% yield (entry 9), whereas reducing the amount of NEt_3 to 3 equivalents provided 72% yield of **10a** (entry 10). Further efforts to lower the amount of NEt_3 failed to improve the yield (entries 11 and 12). Changing the relative amounts of aldehyde and DHF from 3:1 to either 2:1 or 1:1 resulted in reduced yields (entries 13 and 14). Other solvents such as dioxane and methylene chloride also failed to improve the product yield (entries 15 and 16).

Table 2 Decarboxylation Conditions Screenings



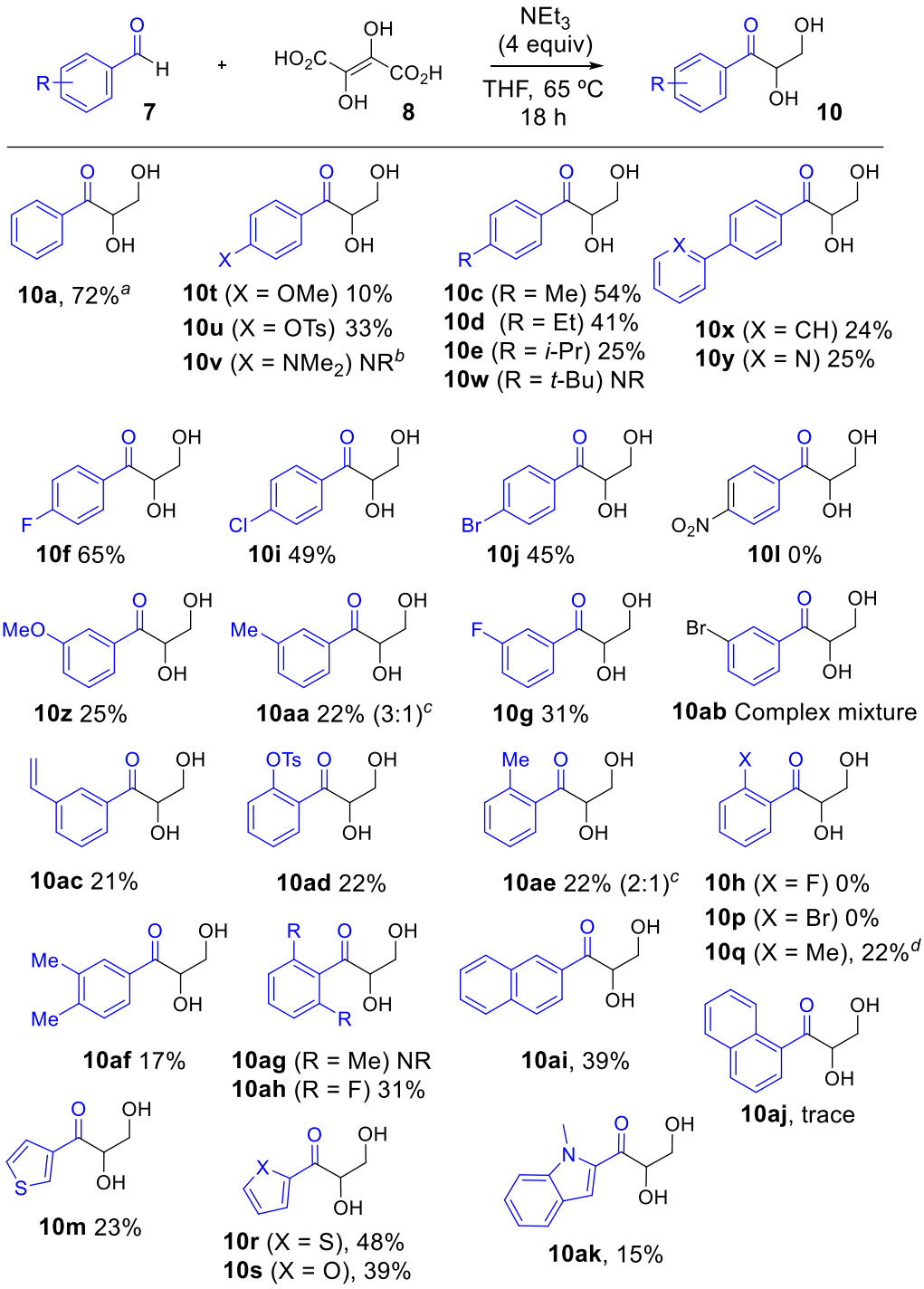
Entry	7:8	Base (equiv)	Solvent (Temp)	Yield (%)
1	3:1	None	THF (23)	Trace
2	3:1	None	THF (65)	15
3	3:1	*i*-Pr_2NEt (4)	THF (65)	25
4	3:1	DBU (4)	THF (65)	--[c]
5	3:1	NEt_3 (4)	THF (65)	68
6	3:1	NEt_3 (6)	THF (65)	62
7	3:1	NEt_3 (3)	THF (65)	72
8	3:1	NEt_3 (2)	THF (65)	64
9	3:1	NEt_3 (1)	THF (65)	55
10	2:1	NEt_3 (4)	THF (65)	45
11	1:1	NEt_3 (4)	THF (65)	28
12	1:3	NEt_3 (4)	THF (65)	trace
13	3:1	NEt_3 (4)	DCM (40)	23
14	3:1	NEt_3 (4)	1,4 dioxane (100)	20
15	3:1	NaOH (4)	THF (65)	--[d]
16	3:1	NaOMe (4)	THF (65)	--[d]
17	3:1	Cs_2CO_3 (4)	THF (65)	--[d]
18	3:1	TBAOH (4)	THF (65)	--[d]
19	3:1	K_2CO_3 (4)	THF (65)	--[d]

20	3:1	KOH (4)	THF (65)	--[d]
21	3:1	NaOH (1M 2mL)	THF (23)	--[d]
22	3:1	NaOH (1M 2mL)	1,4 dioxane (100)	--[d]

[a] Reaction performed with indicated amounts of benzaldehyde **7a**, DHF (**8**), and base in indicated solvent at the listed temperature. [b] Isolated yields after column chromatography. [c] Formation of benzoic acid via Cannizzaro-type oxidation of 7a. [d] No desired product. Degradation of DHF observed.

3.3 Examination of Substrate Scope of the Decarboxylation Reaction.

Having optimized the conditions for the decarboxylation reaction with benzaldehyde, the scope and limitations of the transformation were initially examined with the same substituted aryl aldehydes that were previously utilized in the deoxalation study (Figure 22). Whereas no deoxalation product was formed with 4-anisaldehyde (**8b**), a 10% isolated yield of decarboxylation product **10b** was obtained under the triethylamine conditions. 4-Methyl-, 4-ethyl-, and 4-isopropyl-benzaldehydes (**8c**-**e**) gave dihydropropiophenones **10c**-**e** in 54%, 41%, and 25% yield, respectively.



[a] Reaction performed with 3 equiv NEt_3.

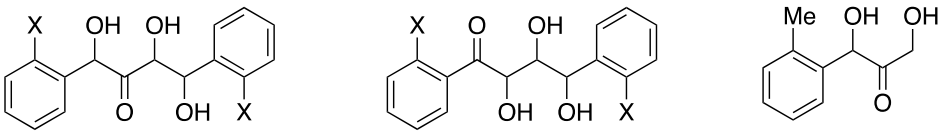
[b] No Reaction (NR)

[c] Parenthesis represents ration of **1** to its ketone regioisomer.

[d] 2:1 mixture of **10q** and its dihydroxyacetone isomer **17q**

Figure 22 Decarboxylation Substrate Scope

For the mono-substituted fluorobenzene series, 4-fluoro- and 3-fluoro-benzaldehydes (**8f** and **8g**) provided decarboxylation products **10f** and **10g** in 65% and 31% yield, respectively. A complex mixture of the isomeric diaryl trihydroxybutanones (**16h** and **17h**) was obtained with 2-fluorobenzaldehyde (**8h)** (Figure 23). Despite using excess aldehyde, this was the first instance that double aldol addition products were observed under our conditions. Intrigued by the observation of the double aldol addition products, we employed 2-bromobenzaldehyde (**8p**) and 2-tolualdehyde (**8q**) and to probe steric and electronic effects. 2-Bromobenzaldehyde gave a similar complex mixture of double aldol isomers (**15p** and **16p**) as seen with the 2-fluoro derivative. 2-Tolualdehyde instead produced 22% yield of a 2:1 mixture of carbonyl isomers **10q** and **17q**. Beyond these complex substrates, 4-chloro- and 4-bromobenzaldehydes (**8i**-**8j**) were more amendable and each gave their respective dihydroxypropionones **10i**-**10j** in 49% and 45% yield.



15h (X = F)
15p (X = Br)

16g (X = F)
16p (X = Br)

17q

Figure 23 Dihydroxyacetone and Isomeric Diaryl Trihydroxybutanone Productions

Interestingly, products **10k** and **10l** were not observed with 4-CO_2Me- and 4-NO_2-benzaldeyde (**8k** and **8l**). Instead, only reduction to form benzyl alcohols **18k** and **18l** were observed (Figure 24). The benzyl alcohols do not arise from Cannizzaro reactions as there are no hydroxide (or alkoxy) bases present. Therefore, DHF must be playing a direct role in their formation.

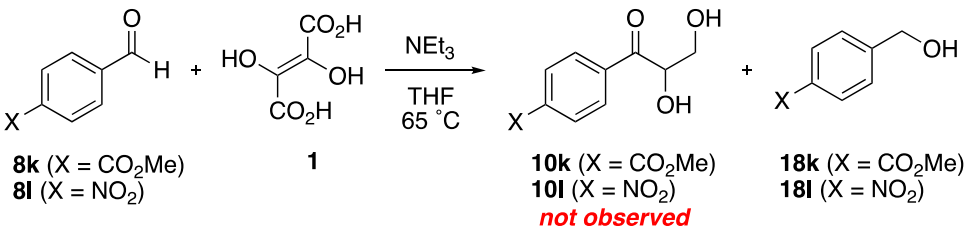


Figure 24 Unexpected Aldehyde Reduction

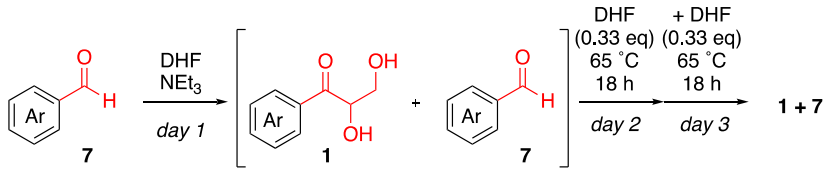
Heteroaryl aldehydes were next explored, but proved troublesome upon initial screening; substantial degradation of starting materials and/or products was observed and no dihydroxypropanone products were detected. After some optimization, it was found that products could be isolated when the reaction was performed in CH_2Cl_2 at reflux. Under these conditions, 3-thienyl-, 2-thienyl-, and 2-furyl-2,3-dihydroxypropionones (**10m**, **10r**, and **10s)** were obtained in 23%, 48%, and 39% yield, respectively. In contrast, nitrogen-containing heteroaryl rings were problematic for the method. Reduction to the benzyl alcohols took place with both pyridine-2-carbaldehyde (**8n**) and 1-formyl-β-carboline (**8o**).

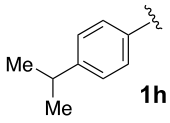
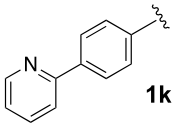
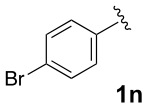
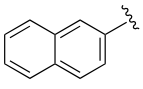
3.4 Cycling of Decarboxylation Reaction

Given the competing self-condensation of DHF, the majority of the aldehyde remains unreacted and can be completely recovered. In order to improve the decarboxylation cascade and amplify the product yields, an iterative decarboxylation cascade process was explored to convert the unreacted aldehyde to more desired product (Table 3). Four representative substrates (**7h**, **7k**, **7n**, and **7ba**) were each subjected to the standard reaction conditions. To each reaction, an additional equivalent of DHF was added after the initial 18 h and the reaction was resumed for another 18 h. This was repeated for another 18 h until a total of 3 equivalents of DHF had been added to the reaction- resulting in an overall 1:1 reaction stoichiometry of DHF to aldehyde. Further additions of DHF over more days resulted in undesired double addition products **11** and **12**. For 4-isopropyl

benzaldehyde **7h**, dihydroxypropanone **1h** gave 16 mg for a 14% yield after 18 h. After the 3rd day, 42 mg of **1h** (12%) was isolated. Even with the added DHF equivalents and longer reaction times, the majority of unreacted aldehyde was still present. The 3-day yield based on recovered aldehyde starting material (BRSM) was calculated to be 81% for **1h**. Similar results were observed for **7k**, **7n**, and **7ba**. In each case, the tree day yields were lower than the one-day yields. The 3-day BRSM yields for **7k** and **7n** were 67% and 65%, respectively. For 2-naphthaldehyde **7ba**, the 3-day BRSM yield was 95%. Although the amplification approach failed to provide higher yields, it does provide a means to access more material in hand. This approach could be of potential use for discovery chemists may need enough material in hand for compound testing and initial bioactivity determination.

Table 3 Attempts toward Amplification of Decarboxylation Yield



entry[a]	Ar	**1** 1d yield[b] (mg isolated)	**1** 3 d yield[c,d] (mg isolated)	BRSM 3 d yield[c,d,e] (Aldehyde recovered)
1	 **1h**	14% (16 mg)	12% (41 mg)	81% (205 mg)
2	 **1k**	25% (32 mg)	19% (75 mg)	67% (215 mg)
3	 **1n**	45% (60 mg)	30% (121 mg)	65% (121 mg)
4	 **1ba**	39% (46 mg)	20% (75 mg)	95% (198 mg)

[a] Reaction performed with aldehyde **7** (3 equiv), DHF (1 equiv), and NEt_3 (4 equiv) in THF at reflux for 18 h. [b] Isolated yields after column chromatography after 18 h reaction. [c] DHF (1 equiv) added at 18 h and again (1 equiv) at 36 h. [d] Isolated yields after column chromatography after 54 h (2 iteration of DHF addition). [e] BRSM yield represents 3-day yield based on recovered aldehyde.

3.5 Application of the Decarboxylation: Synthesis of C-Veratroylglycol.

Aryl 2,3-dihydroxypropionones (**10**) represent a class of highly oxidized alkyl chains that have garnered the attention of synthetic chemists for many years.[45] They represent a diverse set of compounds that include both pharmaceutically-relevant lignan and non-lignan natural products and synthetically-derived compounds.[46] Despite the prevalence of (hetero)aryl 2,3-dihydroxylpropionones in nature, only a small subset has been examined for biological activity due to the low abundance of the individually isolated compounds.[47] For instance, *C*-veratroylglycol (**10t**) is a naturally-occurring 2,3-dihydroxypropiophenone that has been isolated from a variety of plants, fruits, and tree saps. It has been shown to demonstrate modest antioxidant,[48] antiproliferative (against human colon cancer cells),[49] and COX-2 inhibitory activity[50] in various studies. The key issues in studying the activity of **10t** are its low abundance in natural sources which gives rise to poor isolated yields. For example, <75 mg can be isolated from 1 kg of hazelnut shells after extensive grinding, milling, sequential extractions, and column fractionations.[34] Similarly, while one study reported that 1.5 mg of **10t** was isolated from 20 L of maple syrup, another claimed that only 0.5 mg was obtained from 1 kg of syrup.[35] *C*-Veratroylglycol can also be purchased primarily from contract companies at a cost of >$100/mg.[36] Therefore, a cheaper approach toward *C*-veratroylglycol would be an enabling endeavor for the scientific community.

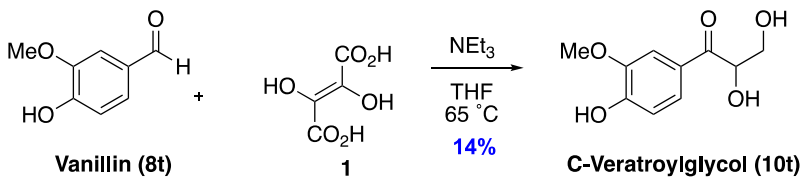


Figure 25 One-Step Decarboxylative Synthesis of *C*-Veratroylglycol

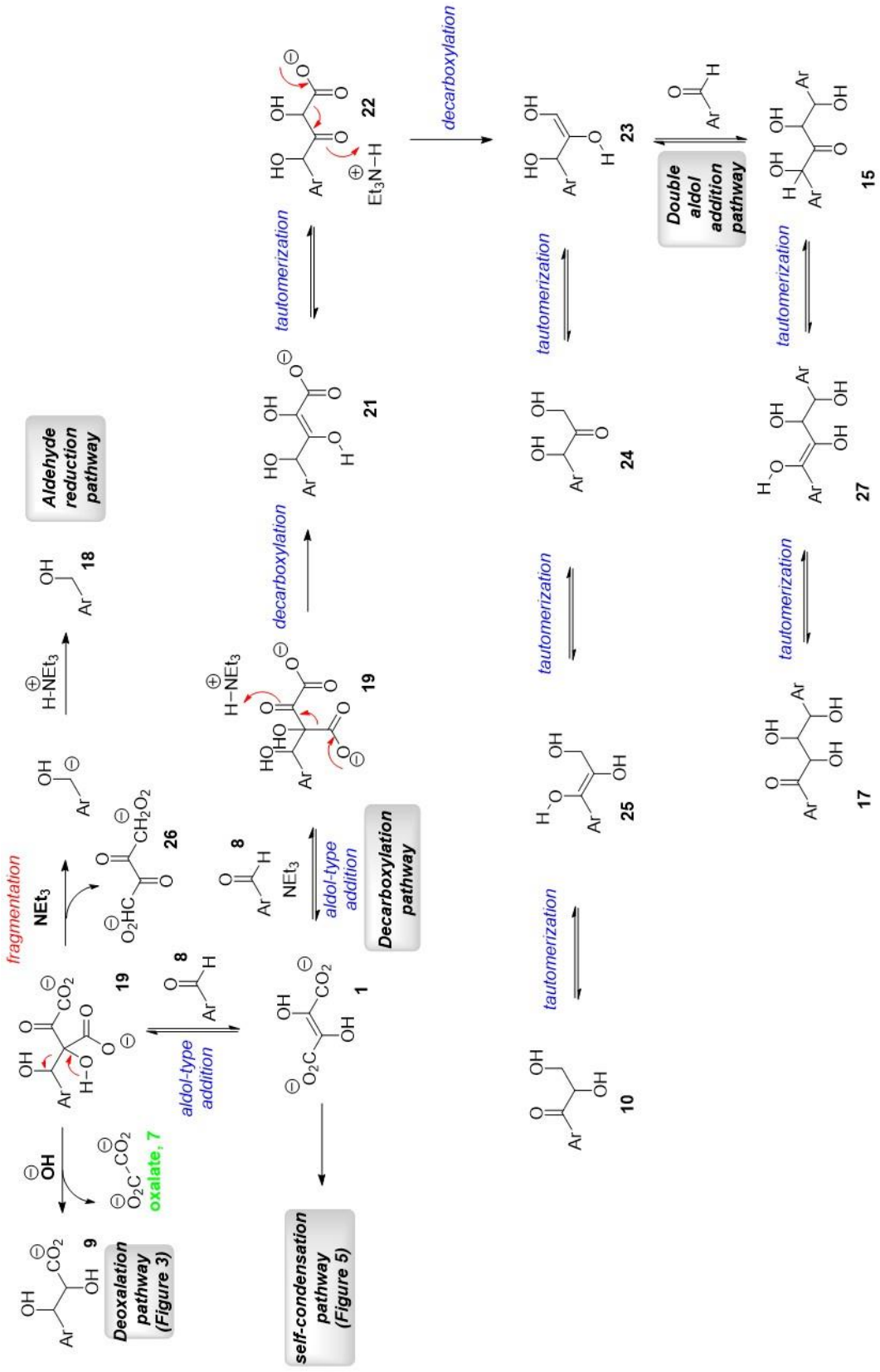
We were pleased to find that the reaction of vanillin (**8t**), DHF, and triethylamine (7 equivalents) afforded *C*-veratroylglycol (**10t**)[37] in 14% yield from the single step reaction (Figure 25). One true value of this decarboxylation approach lies in the financial savings. Based on raw material and solvent pricing, we can synthesize 25-30 mg of *C*-veratroylglycol for ~$2.36/mg, which is ~50-fold cheaper than purchasing it from current commercial sources. To complement this synthesis, we have begun to assemble a small compound library of various substituted aryl 2,3-dihydroxypropionones by using the decarboxylation method.

3.6 Complete Mechanistic Picture of Chemodivergence.

The complete mechanistic landscape for the reactions of DHF with aryl aldehydes is shown in Figure 26. The reaction can take place along various pathways depending on the choice of base, solvent, and the electron-donating or electron-withdrawing substituents on the aryl aldehyde component. Upon aldol addition of DHF to the aldehyde to form intermediate **19**, three possible pathways for fragmentation are plausible. In the first pathway, nucleophilic attack on the carbonyl by hydroxide occurs. Subsequent deprotonation (mediated by hydroxide) leads to the deoxalative fragmentation pathway to generate 1-aryl 2,3-dihydroxypropionates **9** (Figure 26). In the second pathway, NEt_3 mediates the transformations as a proton transfer agent (NEt_3/$^+NEt_3H$). Following aldol addition of DHF, aldol addition intermediate **19** then undergoes decarboxylation to form enediol **21**. NEt_3-mediated tautomerization provides **22** followed by another decarboxylation to form enediol intermediate **23**, which can tautomerize to dihydroxyacetone **17**. Further isomerizations mediated by NEt_3 and its conjugate acid

provide the observed 2,3-dihydroxypropionone **10**. Alternatively, a second aldol-type reaction can take place between enediol **23** and another aldehyde molecule to provide diaryl trihydroxybutanones **15** and **16** (after carbonyl isomerization). This second addition arises when the isomerization from **24** to **10** is slower than tautomerization to enediol **23**. In the cases of electron-poor arenes with NEt_3, fragmentation of intermediate **19** can occur such that a resonance-delocalized benzylic anion is generated along with 2,3-dioxosuccinate (**25**). Subsequent protonation yields the alcohols **18**. The major impediment toward higher yield is presumably the complications that can result from self-condensation of DHF.

Figure 26 Integrated Mechanistic Proposal for Product Formation



3.7 Conclusions

In summary, through a combination of control reactions and DFT calculations, we have demonstrated that DHF is nucleophilic in its dicarboxylate form and electrophilic in both its free acid form and when derivatized as a diester. The DHF dicarboxylate, under the high pH conditions, readily undergoes self-condensation to afford tartronic acid, glycolic acid, and tartaric acid. In contrast, the diester is completely stable and unreactive even at elevated temperatures, while the free acid undergoes very slow self-condensation. This represents the first efforts to understand and codify the reactivity of DHF in order to harness its greater synthetic potential.

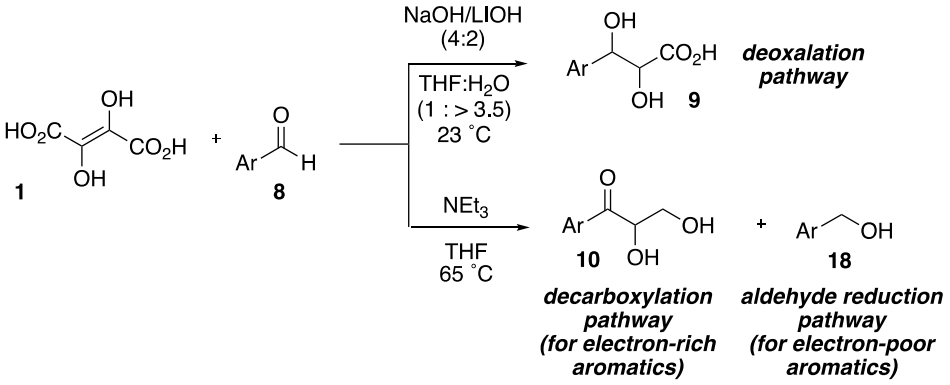


Figure 27 Summary of DHF Chemodivergence

In particular, the reactions of DHF with aryl aldehydes display remarkable base-mediated chemodivergence (Figure 27). With excess hydroxide in a THF: H2O (1:47) mixture, DHF reacts with aryl aldehydes by aldol addition followed by a deoxalative fragmentation to form 3-aryl-2,3-dihydroxypropionates. The propionates were isolated as their methyl esters in up to 64% yield following esterification of the crude mixture. The nature of the base used to form the dicarboxylate plays a central role in the nucleophilic reactions of DHF. Hydroxide acts as both a base and a nucleophile to promote deoxalation.

Conversely, with excess NEt_3 in THF, the same aldol intermediate undergoes a series of decarboxylations and carbonyl isomerizations to form 1-aryl-2,3-dihydroxypropionones in up to 72% yield. NEt_3 acts as a proton shuttle to mediate the various transformations. Compared to the literature precedent for the DHF reaction with aryl aldehydes (which predominantly forms substituted dihydroxyacetones or the disubstituted trihydroxybutanones), selective formation of the 1-aryl-2,3-dihydroxypropionones is achieved. The overall reaction represents a formal C(sp^2)-H alkylation of an aldehyde to form the propanone products. In both cases, the reaction is generally amenable to 3- and 4-substituted benzaldehydes, although strongly electron-rich substituents give very low yields or no reaction at all. While strongly electron-withdrawing substituents are tolerable in the deoxalation reactions with hydroxide, the desired propanones are not formed with NEt_3 and reduction to the corresponding benzyl alcohols are observed instead. Heteroaryl aldehydes are amenable to the deoxalation reactions but those containing basic nitrogens give reduction products or other side reactions with NEt_3. Finally, in an application of the decarboxylation method toward target synthesis, *C*-veratroylglycol- an expensive, bioactive, and naturally-occurring 2,3-dihydroxypropiophenone- was synthesized cheaply in one step from vanillin with a 14% overall yield.

3.6 Follow Up Project

With the ability to synthesis *C*-veratroylglycol in hand via the novel DHF base promoted decarboxylation we set out to apply this synthesis to a collection of different natural products derived from *C*-veratroylglycol. While it only has modest bioactive properties but other natural products based on it are better. Compounds such as

wikstroemone[34] and icariol A_1[35] as well as other lignan natural products could be accessed much easier with the more rapid route to *C*-veratroylglycol (Figure 28).

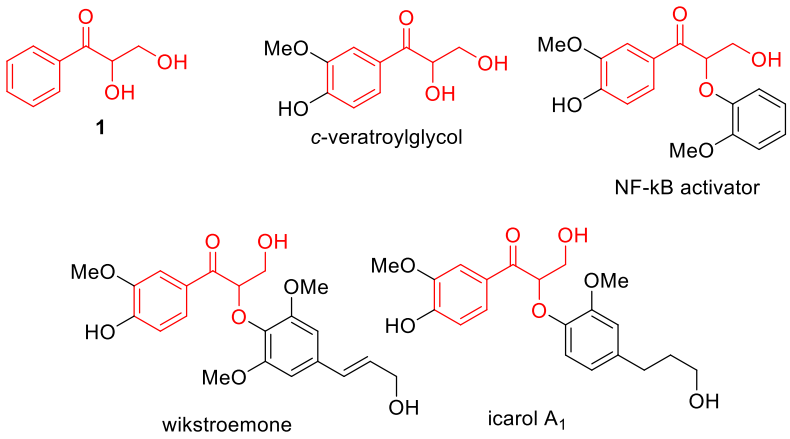


Figure 28 *C*-Veratroylglycol Derived Lignan Natural Products

The retrosynthetic analysis of these two compounds was fairly straightforward (Figure 29). The final product will be formed through a Mitsunobu reaction between the protected *C*-veratroylglycol and whichever protected phenol is necessary to complete the carbon skeleton. The *C*-veratroylglycol will be synthesized through our standard decarboxylation conditions using tosylated vanillin to increase yield and protect the phenol on that portion of the molecule. Each of the two phenols will be synthesized from vanillin and syringaldehyde respectfully. Standard Horner-Wadsworth-Emmons condition to add the rest of the carbon skeleton before the final Mitsunobu reaction.

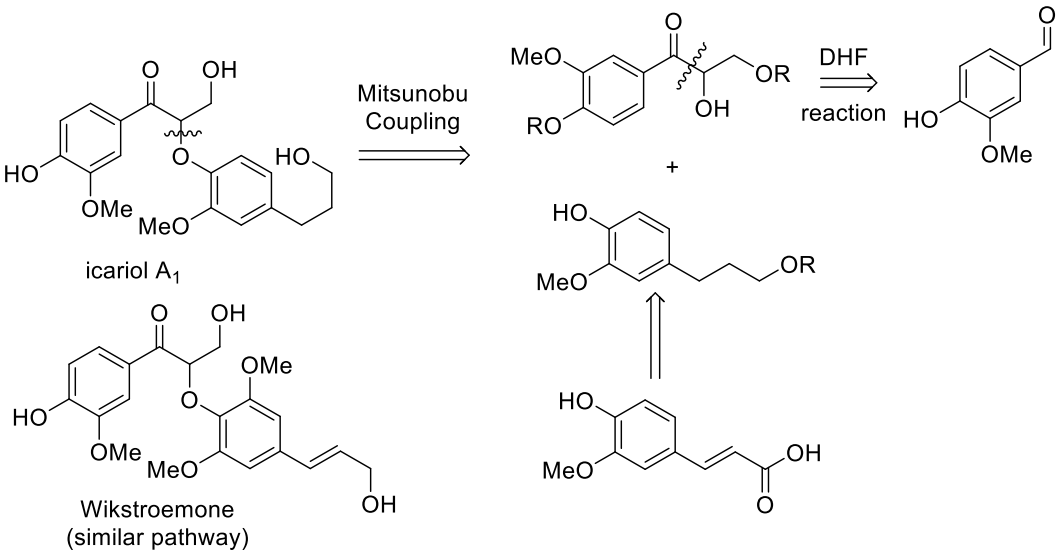


Figure 29 Retrosynthetic Analysis of Lignan Natural Products

The synthesis of wikstroemone and icarol A_1 is currently underway (Figure 30). For the synthesis of *C*-veratroylglycol, vanillin was protected quantitatively with tosyl chloride (**29**) followed by standard decarboxylation conditions to provide the tosylated *C*-veratroylglycol (**10aj**) in 32% yield. TBS- protection of the primary alcohol proceeded cleanly with TEA in DCM at 85% yield (**32**). The phenol portion of wikstroemone was formed through the commercially available product of an HWE olefination between syringaldehyde and the carboxyl phosphonate. Standard LAH reduction of the carboxylic acid followed by TBS protection of the resulting primary alcohol was successful at 53% yield (**33**). For the icariol A_1 phenol portion the synthesis was quite similar. HWE olefination of vanillin followed by and LAH reduction of the pendant carboxylic acid or commercially available for a higher price. Hydrogenation over palladium in MeOH and protection of the primary alcohol with TBS completed the synthesis (**34**).

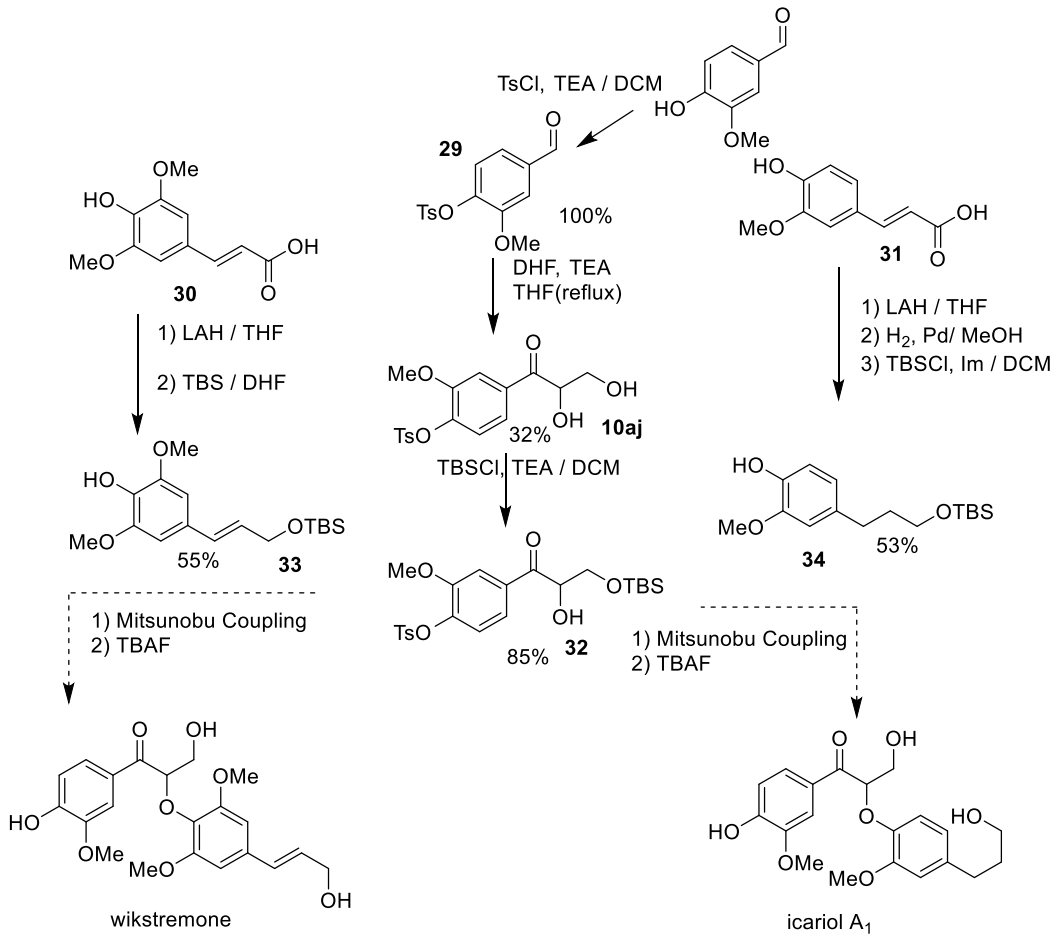


Figure 30 Current Synthesis of Wikstremone and Icariol A_1

The completion of both natural products should be fairly straight forward. The key Mitsunobu coupling may require some optimization as the secondary alcohol of *C*-veratroylglycol is somewhat sterically hindered. Heating or modification of the primary alcohol protecting group would be the first thought for overcoming this issue. Finally, global deprotection by TBAF/Acid would remove all protecting groups and provide the final targets.

If this method of synthesizing lignan natural products such as wikstroemone and icariol A_1 there are several other targets that would be of interest. The *C*-veratroylglycol motif is common within all of these targets. These neolignans differ from the above

synthesized targets at the C-1 position by reduction of the ketone to an alcohol (Figure 31). The various neolignans are particularly attractive targets as they exhibit cytotoxicity to various tumor cell lines at a level similar to cisplatin and 5-fluorouracil.

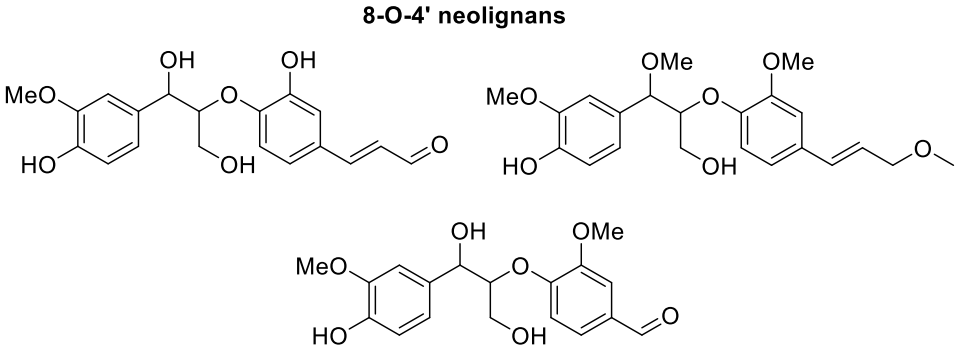


Figure 31 Neolignan Targets

CHAPTER 4: GLYOXYLATE AS A PREBIOTIC LINKER

This chapter presents the study of glyoxylate a possible nucleoside linker is studied. Extensive attempts to synthesize, through standard organic methods, a glyoxylate linked nucleoside are laid out. Both acid and base mediated methods with a range of differing glyoxylate analogs are examined as well as O,S and S,S acetals. A pivot toward a possible novel alcohol protecting group is proposed. Protection and deprotection conditions alongside orthogonality of the new protecting group are examined

4.1 Introduction

The question of how life developed on Earth has vexed man for all time. While many theories have been presented over the years, currently the most widely supported theory is the so-called "RNA World" hypothesis.[51] This theory states that linear chains of ribonucleic acids (RNA) linked through phosphodiester linkages formed the first enzyme-like catalysts that allowed for self-replicating enzymes to form. These nucleic acid strands acted as both the template, through the fidelity of their base-pairing properties, as well as the enzymes to catalyze the polymerization reactions necessary for their reproduction.

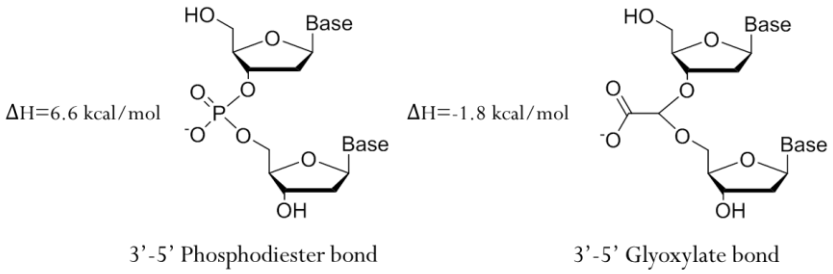


Figure 32 Thermodynamics of Nucleoside Linkages[52]

There are some problems inherent in the theory: the most glaring of which is the fact that forming the phosphodiester linkage between two nucleosides is not an enthalpically favorable process (Figure 32).[52] Each phosphoester bond formed has a ΔH=

3.3 kcal/mol, so a dinucleotide would have a $\Delta H = 6.6$ kcal/mol.[52] Also, experiments stirring the free phosphate and nucleosides in various prebiotic conditions do not show any formation of the dinucleotide. These results suggest that there must have been some RNA precursor polymer that had some type of linkage that was more easily formed and could serve as a template for the formation of the ubiquitous phosphodiester linkage.[52] This template would need to possess a linker that would have existed on prebiotic Earth as well as be able to base-pair with a complimentary phosphate strand.[52]

One of the first suggested linkers replaced the phosphodiester moiety with a peptide bond to link each monomer together. The resulting nucleic acid strand was referred to as peptide nucleic acid (PNA).[53] The main drawback for this model is the substantial difference in electronic structure between the peptide bond and the phosphodiester bond. The peptide bond lacks the negative charge that is present in DNA. This causes it to adopt a substantially different structure than DNA, resulting in stronger binding to itself than DNA. This means that it would probably not be a good template, as it would preferentially interact with another PNA strand instead of serving as a template for the formation of a complimentary strand linked through phosphodiester bonds.

A promising possible linkage molecule is glyoxylate. The Miller-Urey experiment was the first experiment to attempt to recreate the conditions that would have existed in prebiotic Earth.[1] A mixture of small molecules was heated and bombarded with UV light, to simulate solar radiation, and electricity, to simulate lightning strikes. A number of interesting molecules were isolated, including glyoxylate. Since this experiment shows that glyoxylate could have existed in the prebiotic environment, it is a plausible substitute for phosphate. Comparing the thermodynamics of the suggested glyoxylate acetal to the

phosphodiester bond shows it to be a more favorable linkage. While the phosphodiester has a ΔH= 6.6 kcal/mol, the glyoxylate acetal has a ΔH= -1.8 kcal/mol, as seen in figure 1.[51] Hud has shown that drying of an aqueous solution of glyoxylate, thymidine, and various Lewis acids will form both the 5'-3' and 5'-5' dinucleoside in small quantities.[52] The set of conditions that provided the greatest yield was $MgCl_2$ at 85˚C.[52] The structures were confirmed through 2D NMR and mass spectroscopy analysis.[52] Modeling was also performed to investigate what a complimentary pair of glyoxylate linked oligomers should look like (Figure 33).[52] The resulting structure resembles the double helix of RNA as

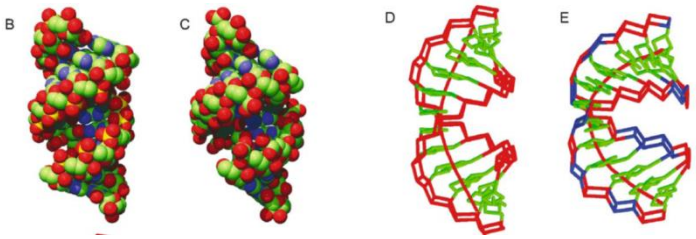


Figure 33 Spacefilling and Stick Models for RNA and gaNA Helices[52]

shown in figure 2.[52] The ga-NA helix is right-handed, just like RNA and has a similar number of bases per turn. Interestingly, it does not have to be diastereotopically pure.[52] Having a mix of *R* and *S* at the acetal position does not significantly perturb the super-molecular structure of the helix.

These glyoxylate acetals have utility beyond the interest in origin of life research. A major application of these functionalities is present in the surfactant industry. Glyoxylate acetals are being used to generate new surfactants and other cleaning agents.[54] When compared to other types of surfactants, glyoxylate acetals are much greener. [54] They also break down easily, which keeps them from polluting the environment, since their breakdown products are not as toxic. One of the current questions in this field is how to form asymmetric acetals as symmetric acetals are all that is currently used.[52] Being able to

have different groups off of the glyoxylate charged portion would allow better tuning of the surfactant's capabilities. While investigating the synthesis of the nucleoside dimers that Hud generated, a mixed glyoxylate acetal system will be generated, and that method can be applied to the synthesis of novel mixed acetal surfactants. We are also interested in expanding the project into the medicinal realm by combining glyoxylate linked nucleosides with therapeutic agents, especially nucleoside analogs. Glyoxylate could also be used in materials by synthesizing polyacetal polymers with glyoxylate linkages instead of the methylene units currently being used.

Our hypothesis is that we will be able to synthesize the different nucleoside dimers (Figure 34) and introduce them into a DNA strand. The three different dimers that will be synthesized are shown in figure 3. The 5'-5' and 3'-3' dimers will be formed mainly to access the desired 5'-3' dimer. Introduction of the 5'-3' dimer should not perturb the overall structure of the DNA and will be able to be read through by polymerases. Also, we intend to attempt to form longer oligomers to study the structure and chemistry of longer chains of glyoxylate linked nucleosides.

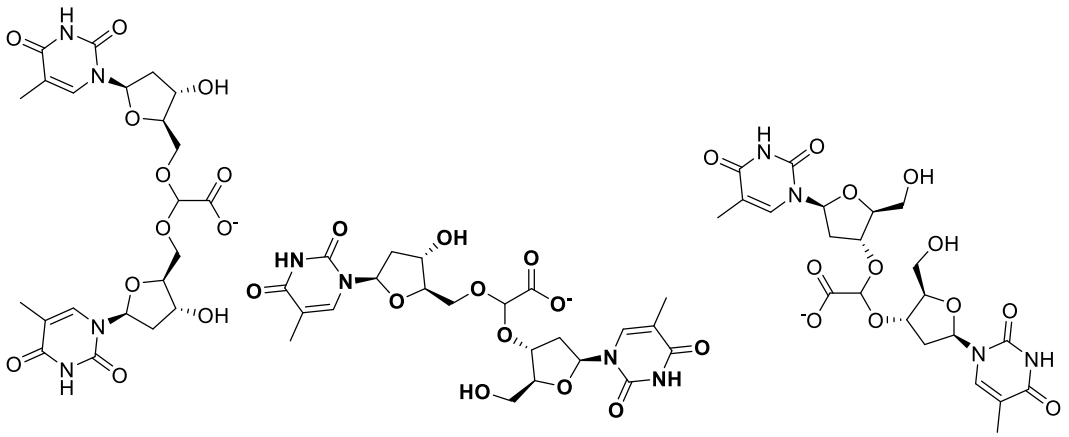


Figure 34 Dimer Targets

4.2 Synthesis of Thymidine Starting Materials

Of the various nucleosides possible, we decided to focus our attention on using thymidine initially. There were several aspects that pointed us toward thymidine: the initial studies done by the Hud lab used it along with the fact that it is the simplest of the extant nucleosides. The lack of a 2' hydroxyl and a nucleobase which required only a single protection made it especially easy to work with. As our goal required both a 5' and 3' free nucleoside, both of these were synthesized cleanly using literature procedures.[55] Starting from commercial thymidine, the 3' free nucleoside was form in two steps (Figure 35). Initial benzylation of the nucleobase using potassium carbonate and benzyl bromide provided the N-Bn thymidine (**35**) in 50% yield. TBS silylation with TBSCl and imidazole resulted in the final product in 78% yield (**36**) or TBDPSCl in 64% yield (**37, 38**). Two different 5' free thymidine derivatives were used in our starting work.

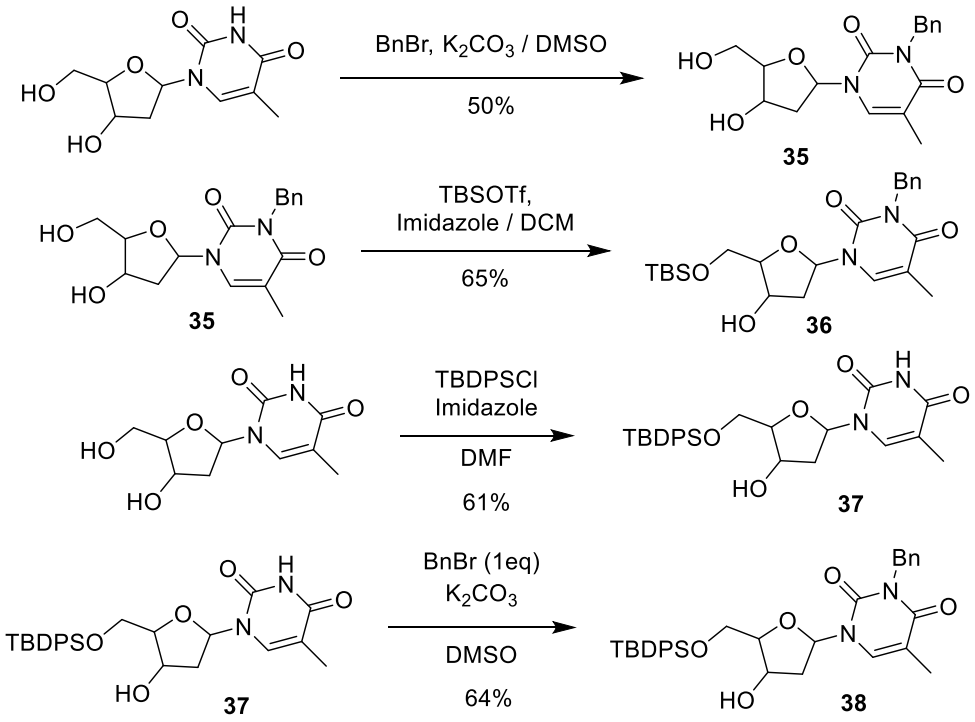


Figure 35 Synthesis of 3'-Free Thymidines

To access 3'-TBS-N-Bn thymidine a four-step process was followed (Figure 36). After similar benzylation of the nucleoside as with the 3' thymidine, reaction with DMTrCl gave 5'-DMTr-N-Bn thymidine (**39**) in 88% yield. TBS protection of the 3' hydroxyl (**40,** 65% yield) and subsequent deprotection of the 3-DMTr (62% yield) provided the desired compound **41**. The 5', N-dibenzyl thymidine was also desired as it is more stable and that was accessed through the 5'-TBDPS intermediate after subsequent exposure to benzylation conditions in an excess of benzyl bromide to form **42** and fluoride deprotection to provide **43**. All products matched previously published literature precedent.

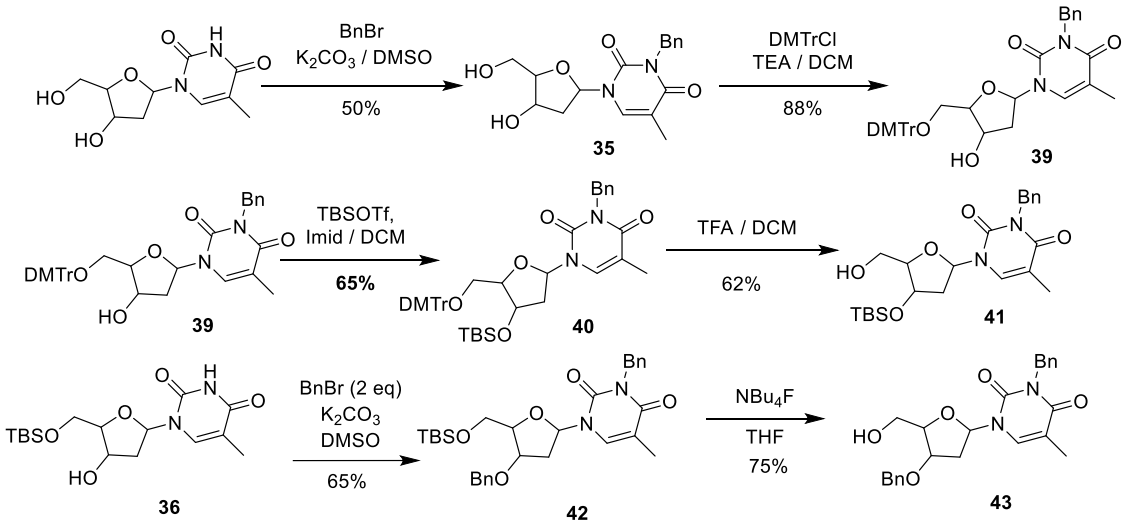


Figure 36 Synthesis of 5'-Free Thymidines

4.3 Initial Dimerization Tests

Our first focus was on dimerization of the 3' substrates with the hope that we could these dimers to effect a transacetalization to provide our desired heterodimers. We set off with standard acetal formation conditions of protic (pTSA) or Lewis (MgCl) acids in the presence of glyoxylate or the glyoxylate methoxy acetal (Figure 37).[56] Even after several

days of reaction these conditions showed no progress and the starting materials were largely recovered. Only small amounts of baseline degradation were observed.

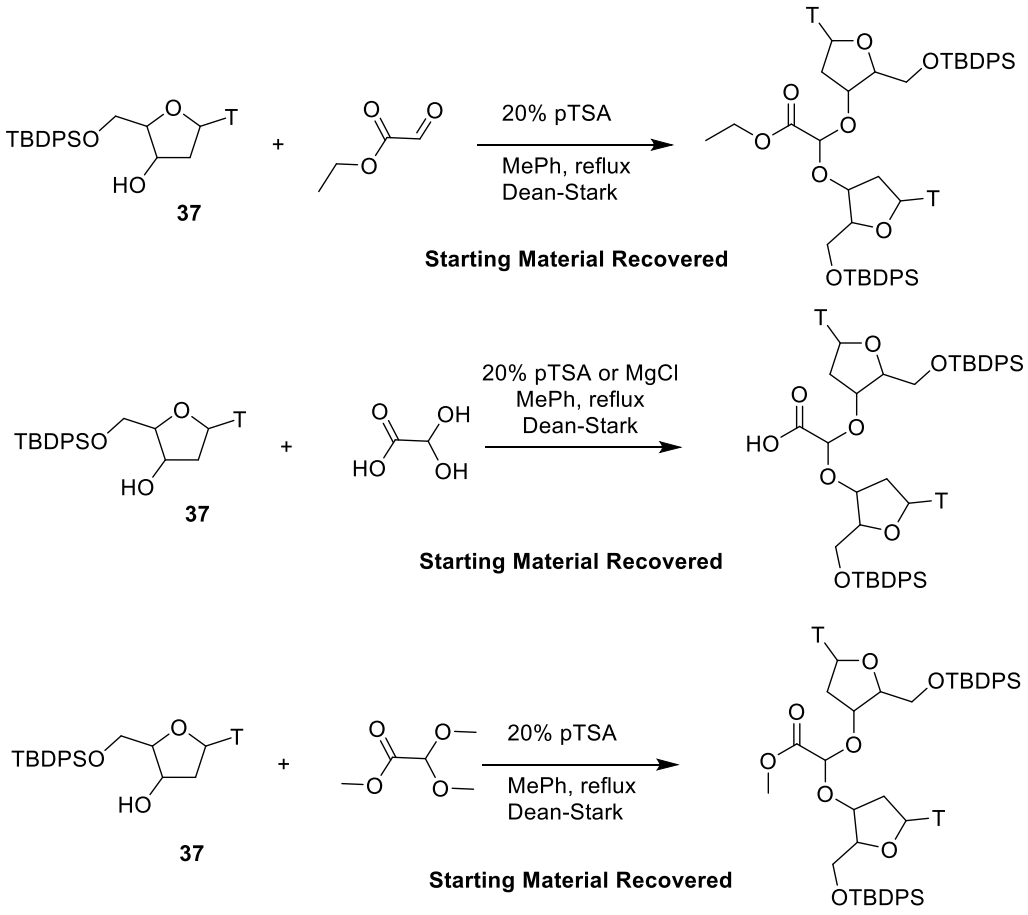
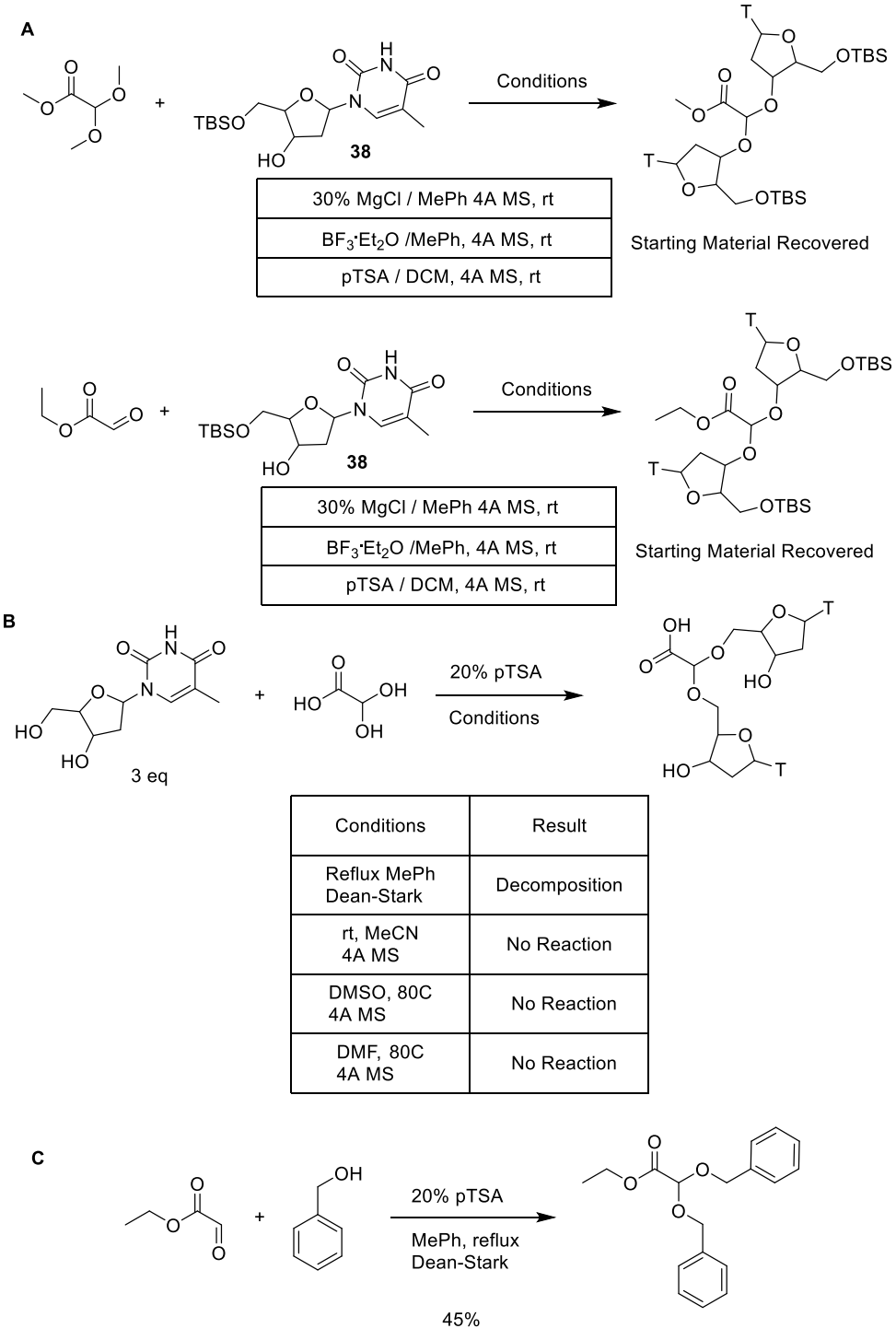


Figure 37 Initial Acid Catalyzed Acetalization

The total lack of any sort of productive reactivity vexed us and after some conversation came up with two possibilities as to why this seem to be. The first was that trying to bring two very large TBDPS protecting groups into such close proximity was creating extreme steric strain and that acid catalysis may be consumed to some extent by the nucleobase leading to weakened reactivity (Figure 38). Moving to 5'-TBS did not improve the reactivity. Under both protic and Lewis acid conditions there was no reactivity either with the methoxy acetal or ethyl glyoxylate (A). Attempts to observe the

dimerization that Hud had reported on a synthetically viable scale using organic conditions also failed with decomposition or no reaction observed by TLC (B). Benzyl alcohol readily reacts with ethyl glyoxylate indicating that there was something about the nucleoside system that was preventing the desired reactivity.



Conditions	Result
Reflux MePh Dean-Stark	Decomposition
rt, MeCN 4A MS	No Reaction
DMSO, 80C 4A MS	No Reaction
DMF, 80C 4A MS	No Reaction

Figure 38 TBS Acetalization and Other Tests

To try to circumvent this we moved away from acid catalysis and moved toward a base promoted S_N2 type method (Figure 39).[57] Using a 5'-TBS substrate we decided to see

if we can form the dimer through reaction with dichloro- methyl acetate in presence of base. Interestingly, if the nucleobase was unprotected we saw substitution at the chloride (**44**) whereas when the nucleobase was benzylated transesterification (**45**) was observed. Even under excess nucleoside the double S_N2 reactivity was never observed. In some cases, the single and transesterification were seen together.

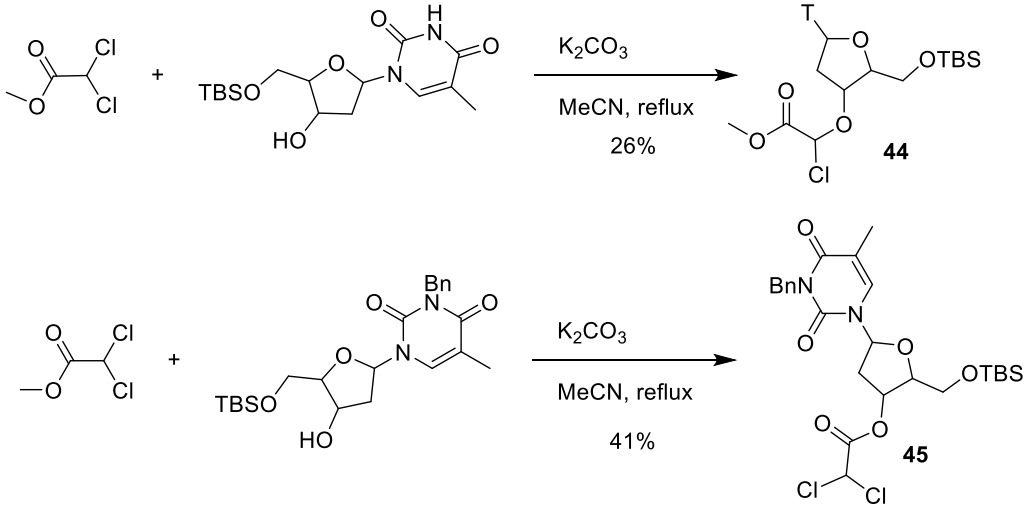


Figure 39 Dichloroacetate Initial Reaction

Rampant transesterification directed us to initially move away from the ester and toward other acetate derivatives that could be converted into the desired carboxylic acid at a later point. A BHT ester was tested first but under the reaction conditions the BHT ester was cleaved (Figure 40).

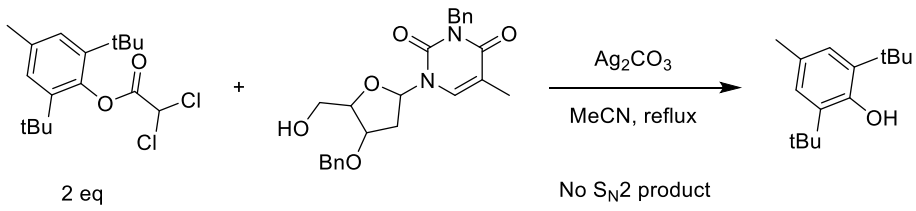


Figure 40 BHT-ester Reactivity

Next was dichloroacetonitrile, which showed more promising results. A quick test reaction with benzyl alcohol indicated that it is amiable toward acetal formation to product the dibenzyloxy **45** (Figure 41). With this positive result we set forward to examine the possibility of nucleoside dimerization.

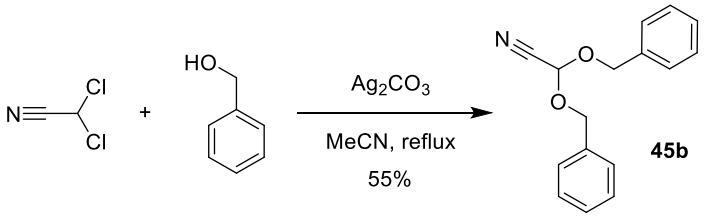


Figure 41 Dichloroacetonitrile Test Reaction

The first attempt at utilizing the dichloroacetate with the nucleosides, the 5' free thymidine (Figure 42), (A) by crude NMR looked to be promising but attempts to purify the homodimer proved futile. Performing the reaction with 5'-DMTr (B) led to migration of the DMTr protecting group while 5- TBS (C) led to a single substitution at mild yield (**46**). Attempts to form the 3' homodimer failed when using excess of nucleoside.

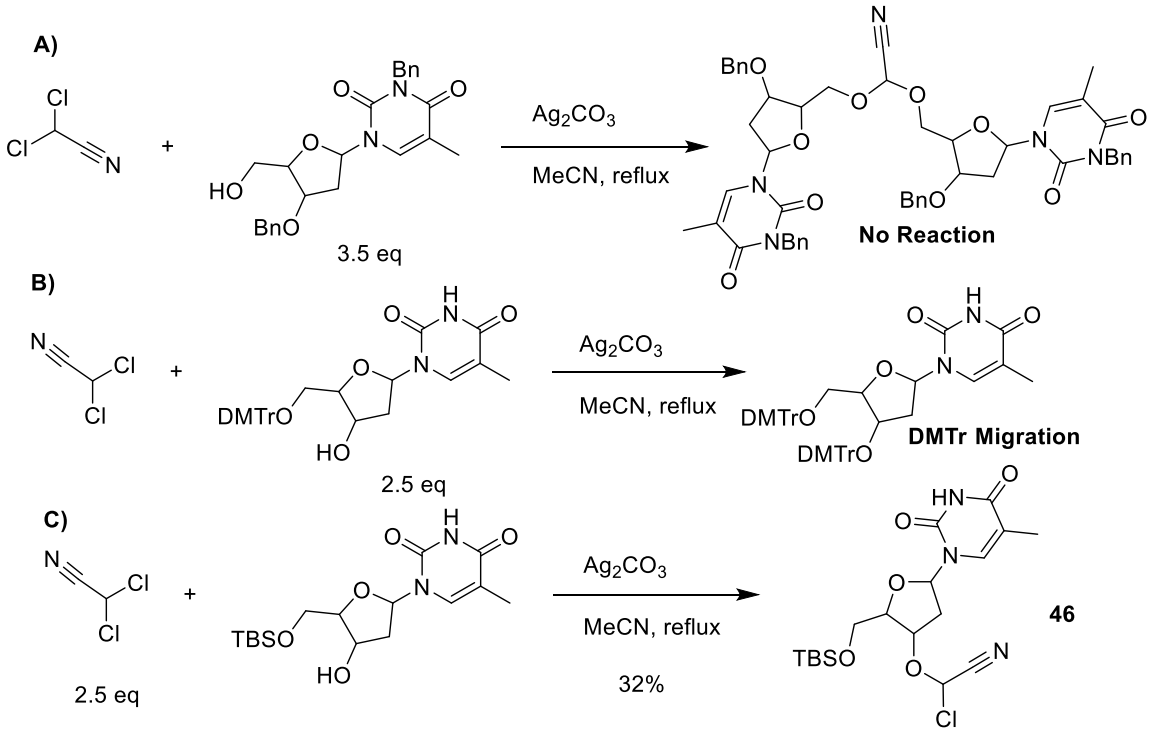


Figure 42 Dichloroacetonitrile Nucleoside Homodimer Formation

Attempts to perform the sequential substitution on the α-chloro product proved futile with either silver or potassium carbonate (Figure 43). Other strong bases were ineffective.

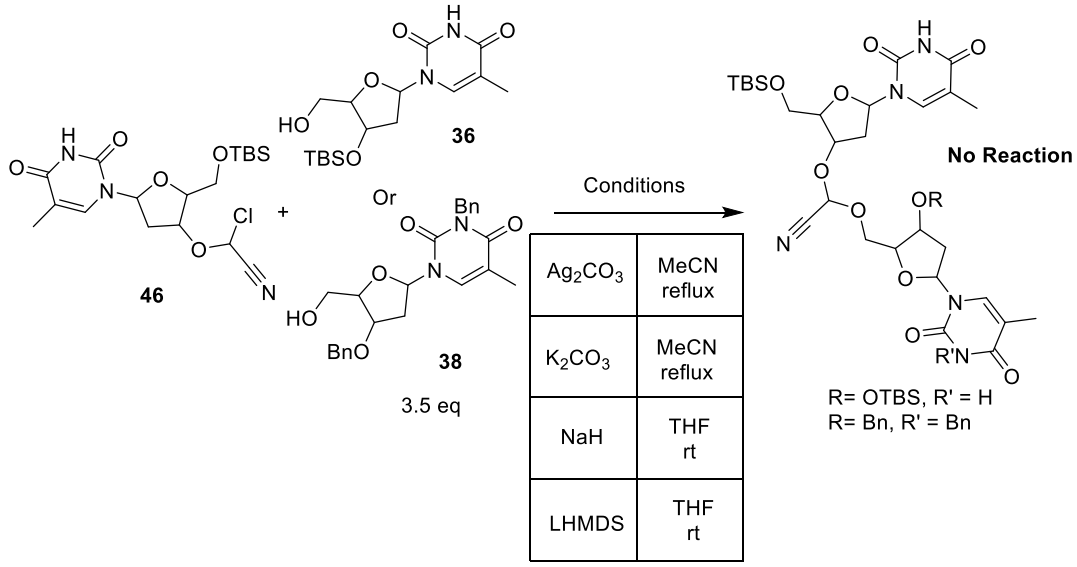


Figure 43 Sequential Substitution Attempts

The complete lack of reactivity toward the 5' free thymidine derivatives made us wonder whether it was possible to even form the homodimer of this less sterically hindered acetal. If this proved ineffective then it would be necessary to determine a completely different route toward the desired target. There was also some concern that the strongly basic conditions that were being utilized could be leading to deprotonation α to the carboxylic acid and shutting down the reactivity. Because of this fluoride promoted methods were attempted to form the alkoxide *in situ* and from there react with the dichloroacetonitrile. CsF with and without a phase transfer catalyst as well as a solution of TBAF proved totally ineffectual at initiating the desired reactivity (Figure 44).

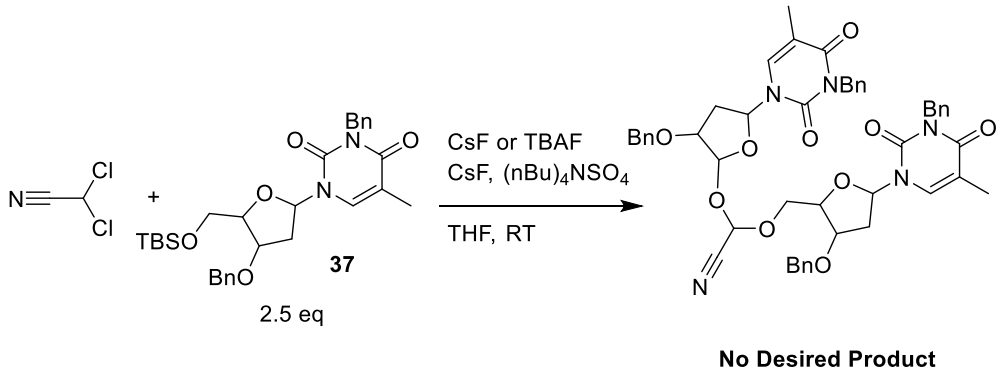


Figure 44 Fluoride Promoted Dimerization Tests

With all of this difficulty, there was a question of whether, in the event that the homodimer was formed, would it be possible to activate it such that transacetalization could occur. The mixed alkyl acetal **47** was formed cleanly in rather low yield of 30% but deprotection and degradation occurred instead of hydrolysis of the acetal under acidic conditions (Figure 45).

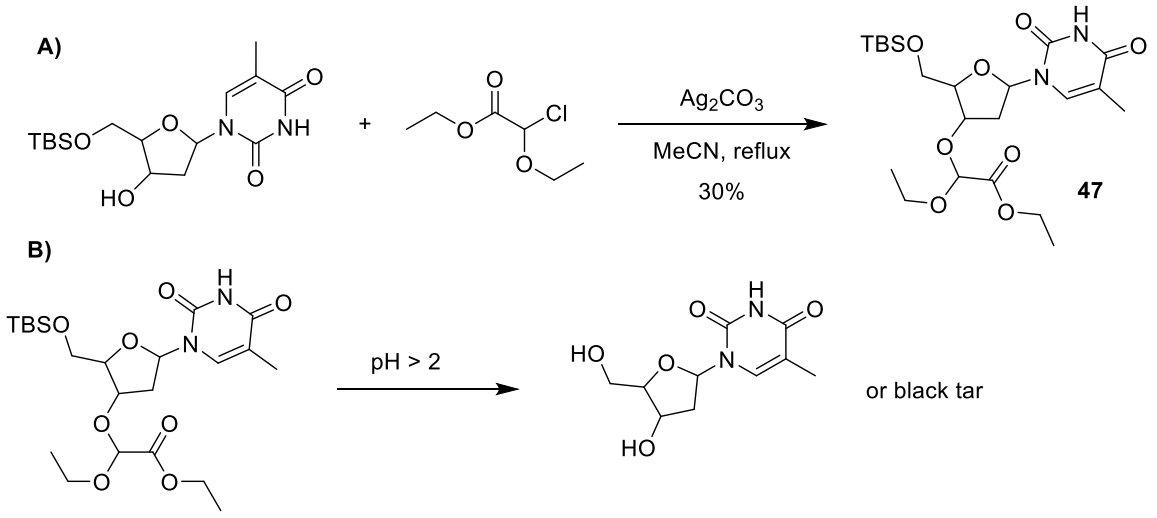


Figure 45 Glyoxylate Acetal Stability

4.4 Glycolaldehyde/dichloroethanol Linker

The surprising stability and intransience of the glyoxylate system suggested that the electron-withdrawing properties of the carboxylic acid moiety could be leading to a detrimental effect on the reactivity. To investigate this, it was hypothesized that the synthesis of these nucleoside dimers could start with a glycolaldehyde or dichloroethanol and after formation of the acetal moiety oxidation would then provide the desired glyoxylate linkage while working around the issues with the carboxylic acid. This had the added benefit of no risk of transesterification occurring. Various protected glycolaldehyde and dichloroethanol derivatives were formed using standard literature methods (Figure 46).

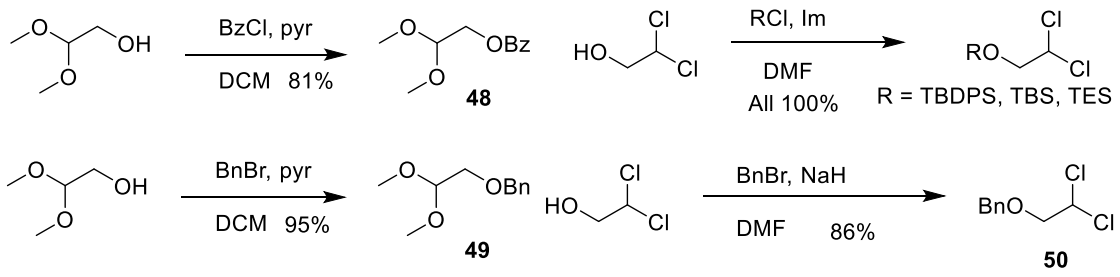


Figure 46 Glycolaldehyde/Dichloroethanol Protections

Various attempts to perform a transacetalization on both the benzyl and benzoyl methyl acetal with different 5' free thymidine derivatives all failed (Figure 47). Along with Lewis acid, protic acid methods were also used but to no avail. In some cases, the free alcohol reacted with the silyl activator, **51,52**. The complete lack of any desirable reactivity directed the work toward the base promoted methods that had shown some possibility of success with the glyoxylate derivatives.

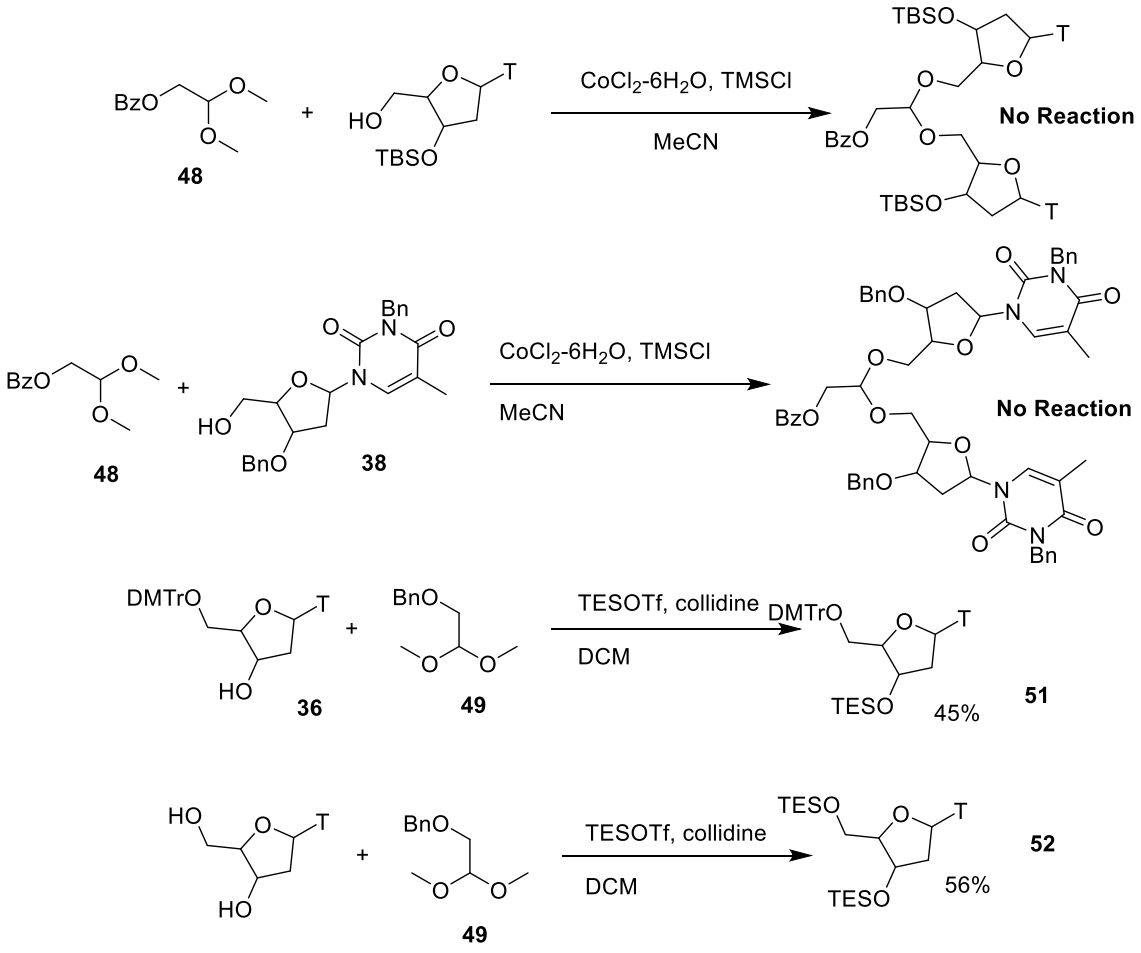
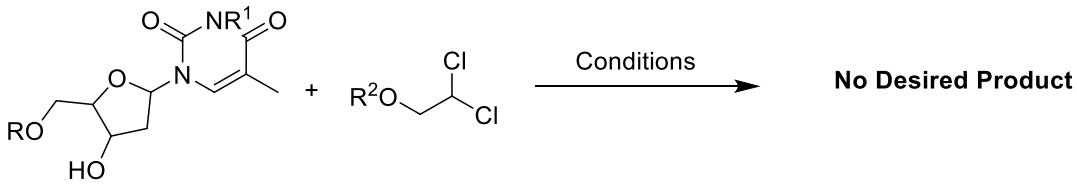


Figure 47 Glycolaldehyde Transacetalizations

A range of different base conditions were used in an attempt to perform the dimerization with both silyl and carbon derived protecting groups throughout the system

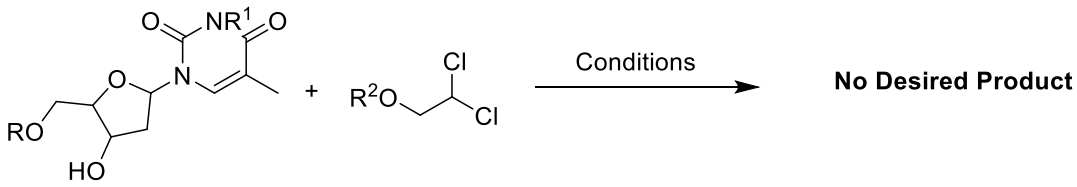
(Table **4**, Table **5**). Initial tests with TBPDS were unsuccessful. It was suspected that the large protecting group could be inhibiting reactivity, but attempts with less sterically bulky protecting groups such as benzyl and alkyl silyl ethers were similarly unsuccessful. This was the case with both 5' and 3' free thymidines. Thymidine with no protecting groups was also tested but to no avail, there was no substitution observed. The starting material thymidine was recovered in all cases.

Table 4 3' Free Thymidine Dichloroethanol Tests



R	R^1	R^2	Base	Solvent	Temp
DMTr	Bn	TBDPS	Ag_2CO_3	MeCN	Reflux
DMTr	Bn	TBDPS	NaH	THF	0°C-rt
TBS	H	TBDPS	Ag_2CO_3	MeCN	Reflux
TBS	H	TES	Ag_2CO_3	MeCN	Reflux
H	H	TES	Ag_2CO_3	MeCN	Reflux
TBS	H	Bn	Ag_2CO_3	MeCN	Reflux
DMTr	H	Bn	Ag_2CO_3	MeCN	Reflux
TBS	H	TES	Hunig's Base, DMAP	DCM	Rt
DMTr	Bn	TES	Hunig's Base, DMAP	DCM	Rt
TBS	H	TES	Hunig's Base	DCE	Reflux
TBS	H	TBDPS	NaH	DMF	0°C

Table 5 5' Free Thymidine Dichloroethanol Tests



R	R^1	R^2	Base	Solvent	Temp
Bn	Bn	TES	Ag_2CO_3	MeCN	Reflux
Bn	Bn	Bn	Ag_2CO_3, AgOTf	DCM	Reflux
H	H	TES	K_2CO_3, KI	MeCN	Reflux
H	H	TES	K_2CO_3, KI	DMF	Reflux
H	H	TBDPS	K_2CO_3, KI	DMF	Reflux
H	H	TBDPS	Ag_2O	MeCN	Reflux
H	H	TBDPS	Cs_2CO_3	MeCN	Reflux
H	H	TBDPS	$AgBF_4$	MeCN	Reflux
H	H	TBDPS	Ag_2CO_3, AgOTf	MeCN	Reflux
H	H	TBDPS	AgOTf	MeCN	Reflux
H	H	TBDPS	NaH	DMF	Rt
H	H	Bn	NaH	DMF	Rt

4.5 O,S Acetal Route

The seeming intransience of the O,O acetal systems directed us toward other possibilities that could both give us a route toward the final target as well as a non-prebiotic analog to be able to study the base-pairing properties of the these glyoxylate linked nucleoside systems. An O,S linked dimer as shown below could be used to determine the base-pairing of the system when inserted into a DNA strand (Figure 48). Instead of having a S-linked nucleoside, an alkyl thiane could be activated by methods that would be more amenable toward formation of the elusive O,O linked nucleoside dimers.

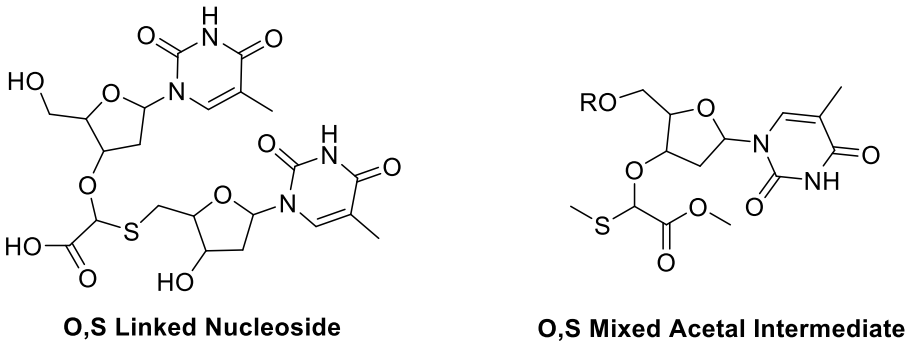


Figure 48 O,S System Overview

The α-chloro, S-Me acetate **53** was synthesized as shown through standard literature methods in high yield. This was then used to form the mixed O,S acetal **54** using the silver carbonate conditions used with the O,O mixed acetals previously (Figure 49). The substitution was clean and the next step was to test different conditions to selectively activate the thioether to allow formation of the oxonium and generate the O,O dimer as desired. Methyl iodide, mercury bromide, and methyl triflate were all unreactive. NIS/TMSOTf and Snyder's Reagent led to deprotection while silver triflate and $NOBF_4$ totally degraded the O,S acetal to baseline (Table 6). A third route to utilize thioethers involved starting with a thiane and deprotecting the aldehyde in the presence of one of the nucleoside monomers with the hope that either the O,S mixed system or O,O homodimer would form (Figure 50). Methylation, unsurprisingly, led to simple methylation of the nucleoside. NBS was unreactive while Snyder's reagent deprotected the silyl group from the nucleoside.

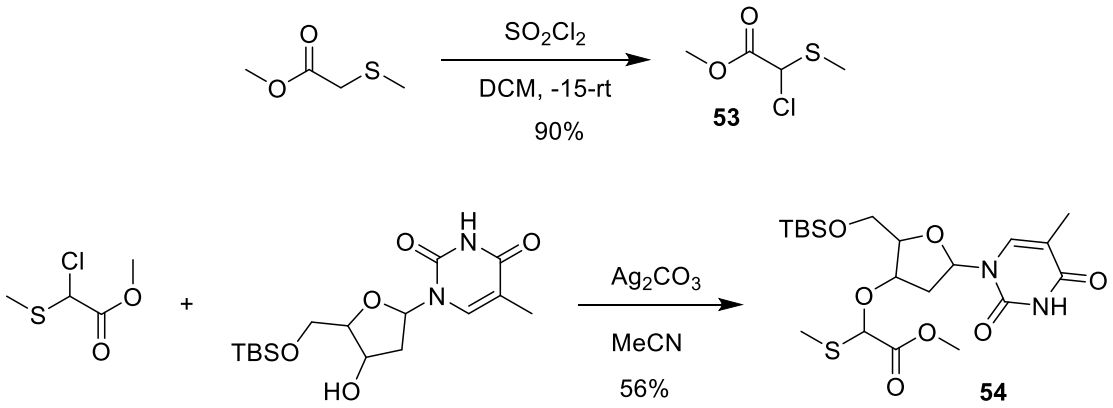
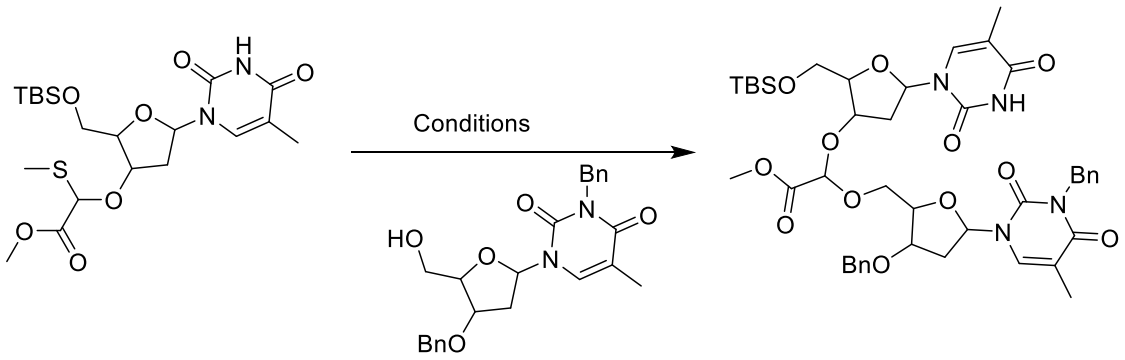


Figure 49 Synthesis of O,S Mixed Acetal

Table 6 O,S Acetal Activation Tests



Activator	Solvent	Result
MeI, K_2CO_3	MeCN, Reflux	No Reaction
$HgBr_2$, HgO	THF, rt	No Reaction
NIS, TMSOTf	THF, rt	Deprotection
NIS, TMSOTf, EtOH	THF, rt	Deprotection
AgOTf, TMSI	MeCN, Reflux	Degradation
Snyder's Reagent	THF, rt	Deprotection
$NOBF_4$	DCM, rt	Degradation
MeOTf	THF, reflux	No Reaction

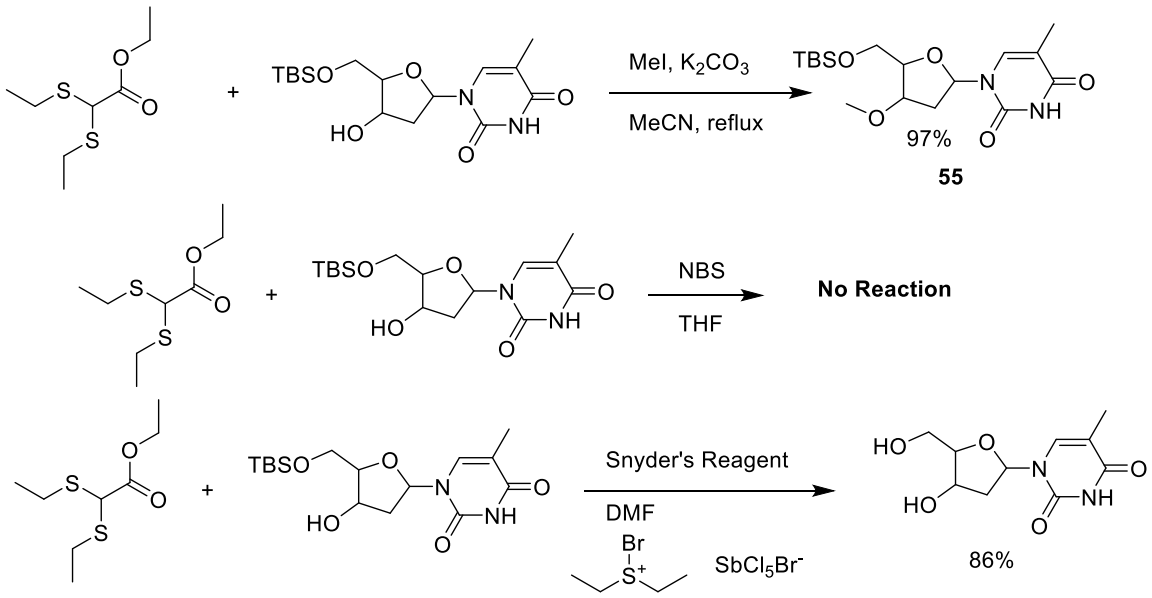


Figure 50 S,S Acetal Deprotections

One final method that was attempted was form the 5'-SH nucleoside and attempting to form the S,S homoacetal with this derivative. The 5-SH nucleoside came from a 4-step literature procedure. Starting from thymidine, the 5'-OH was converted to a tosylate in 61% yield followed by an S_N2 substitution with potassium thioacetate. The 3'-OH was protected with a TBS group and saponification of the thioester provided the desired derivative (Figure 51). Unfortunately attempts to form the S,S homodimer also failed to result in any of the desired product.

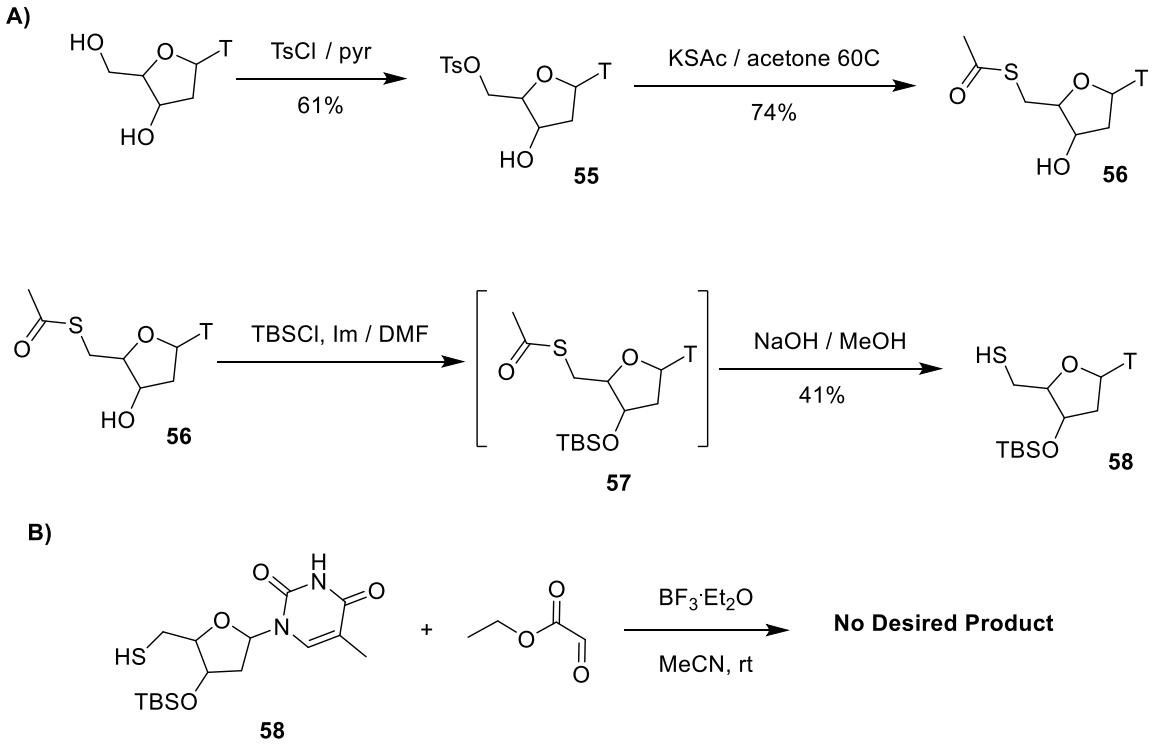


Figure 51 S,S Homodimer Method

4.6 Salvaging a Bad Situation

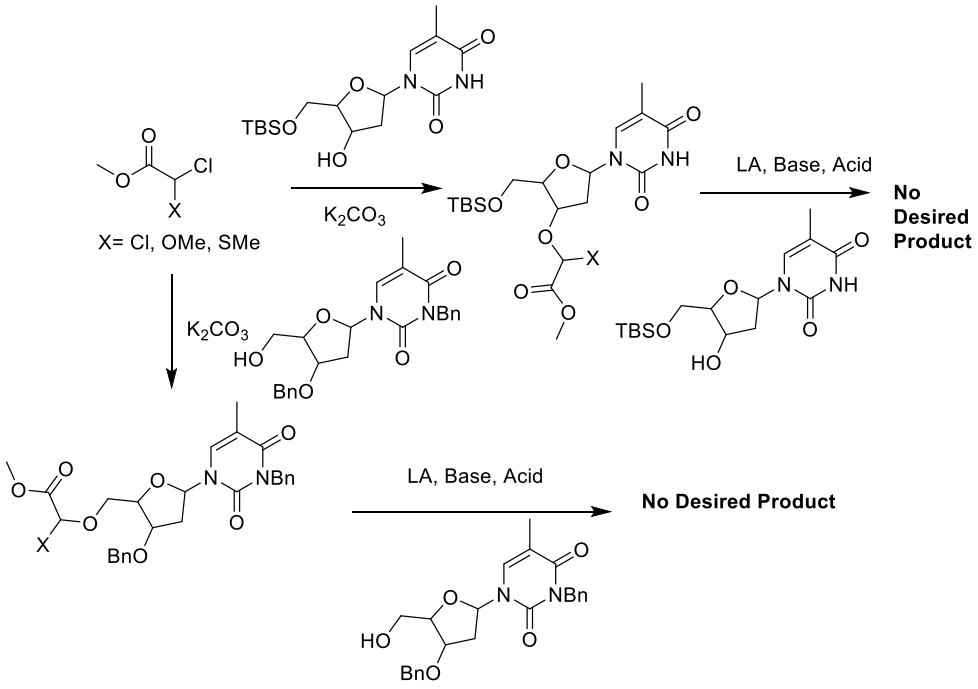


Figure 52 Summary of Glyoxylate Dimer Attempts

In summary, over two years were taken trying to form this seemingly very simple linkage (Figure 52). A wide range of different techniques were used to try to form them. The most vexing part of this work was that the first nucleoside was easily attached but the second failed utterly. With the inherent intractability of the nucleoside-glyoxylate bond it led the thinking toward the possibility of this functional acting as a novel alcohol protecting group. Toward this end, along with Dr. Cynthia Martin, a range of different alcohols were exposed to the reaction conditions (Figure 53). The conditions proved to be somewhat generalizable and allowed for the protection of various alcohols via glyoxylate. Both aryl and alkyl alcohols tolerated the conditions but increasing the steric environment around the alcohol proved to lead to side reactions or complete loss of reactivity.

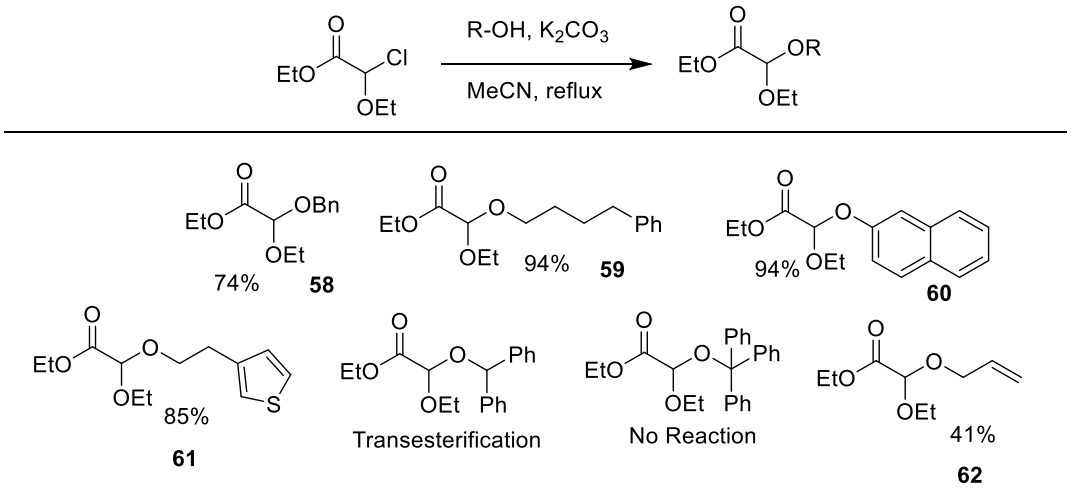


Figure 53 Screening of Alcohol Protection Substrates

Acetals are well known in literature to serve as alcohol protecting groups. Some examples include MOM/SEM, which are linear acetals, as well as cyclic acetals such as tetrahydropyran (Figure 54). These protecting group are most useful as they are easily removed by protic acid treatment. The ease of both applying and removing these types of protecting groups makes them some of the most commonly used in organic chemistry. Unfortunately, while they are very easy use they are not orthogonal. Conditions to remove one will often deprotect all acid sensitive protecting group on the molecule. Adding another protecting group that appears to be both acid and base stable would be of interest to the field at large. With this in mind an attempt was made to determine the best method to for deprotection and then prove that other protecting groups can be selectively

deprotected in the presence of the new glyoxylate acetal protecting group.

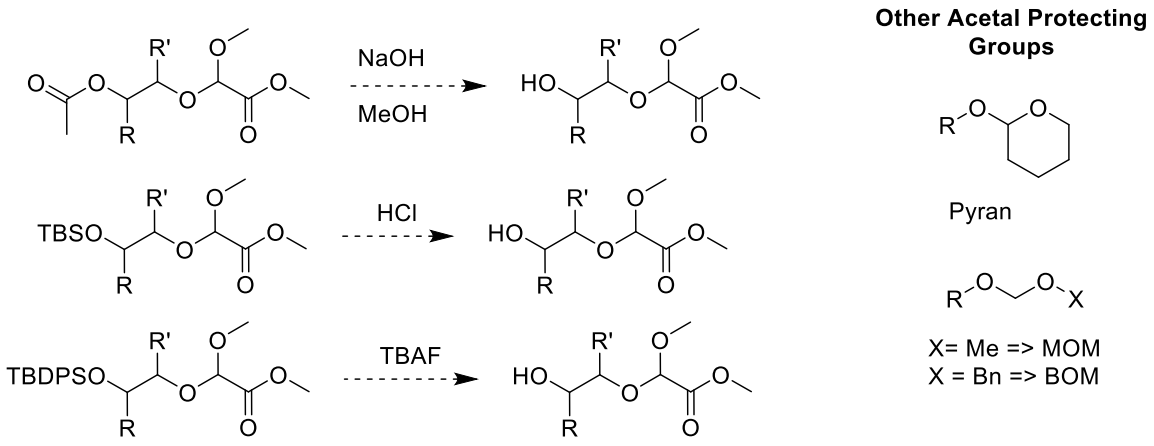


Figure 54 Orthogonality of Glyoxylate Protecting Group

The initial substrate selected to test deprotection conditions was benzyl alcohol (Figure 55). Reacting under the standard conditions provides the deprotection substrate cleanly in 76% yield. To test deprotection selectivity dihydroxy *p*-xylene will be mono protected and a second group will be attached. This will allow for determining the orthogonality of the system.

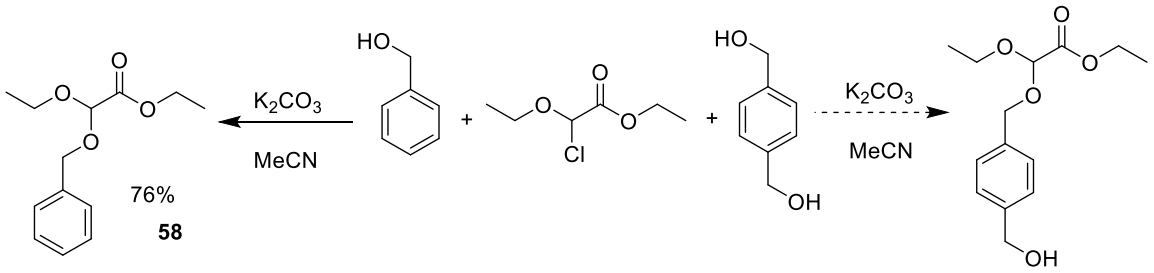
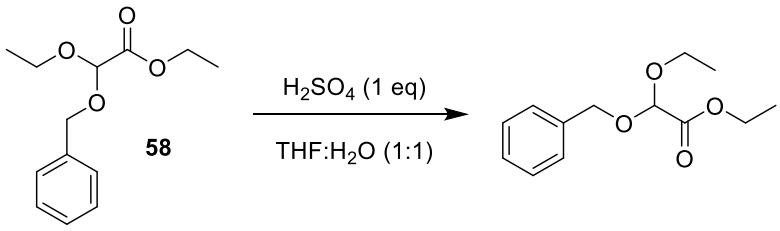


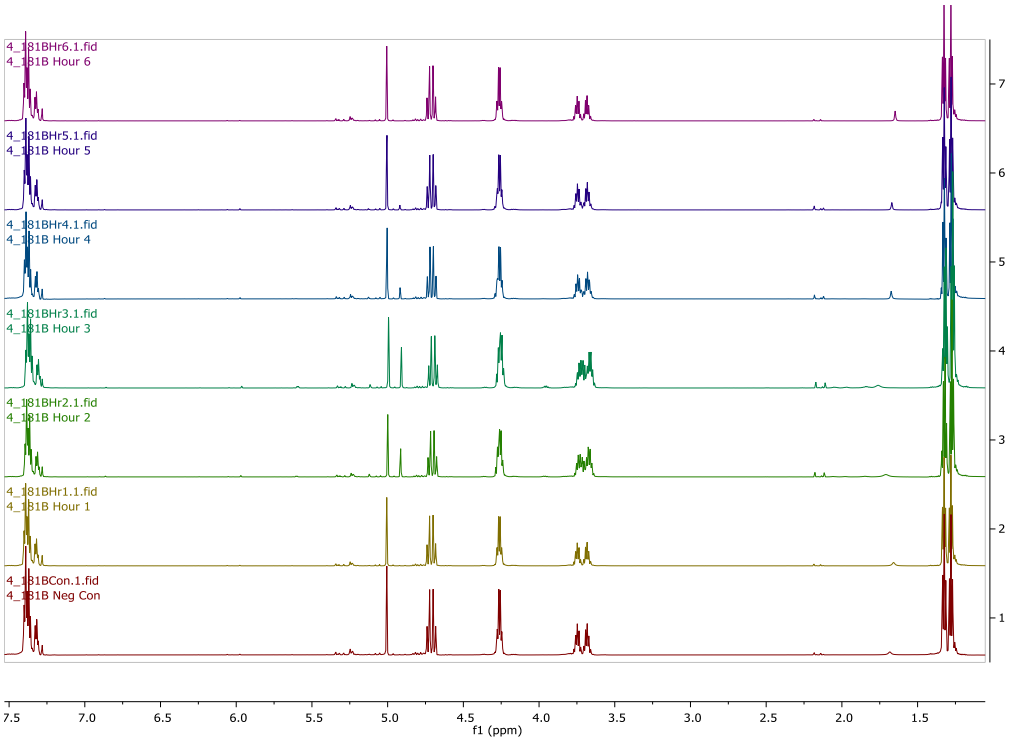
Figure 55 Screening Substrate Synthesis

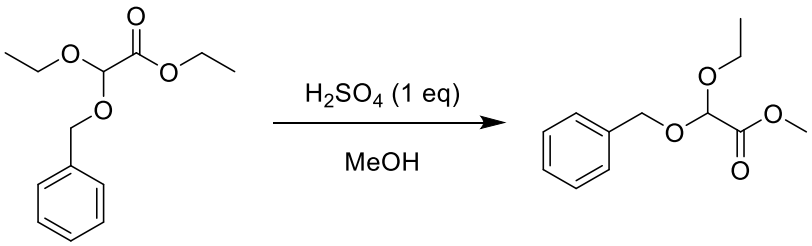
To determine the best route of deprotection the benzyl glyoxylate acetal was exposed to a series of conditions (Figure 56). The progress of the reaction was observed for the production of benzyl alcohol as this would indicate that deprotection had occurred. The substrate was exposed to differing protic and Lewis acid conditions hoping to see some

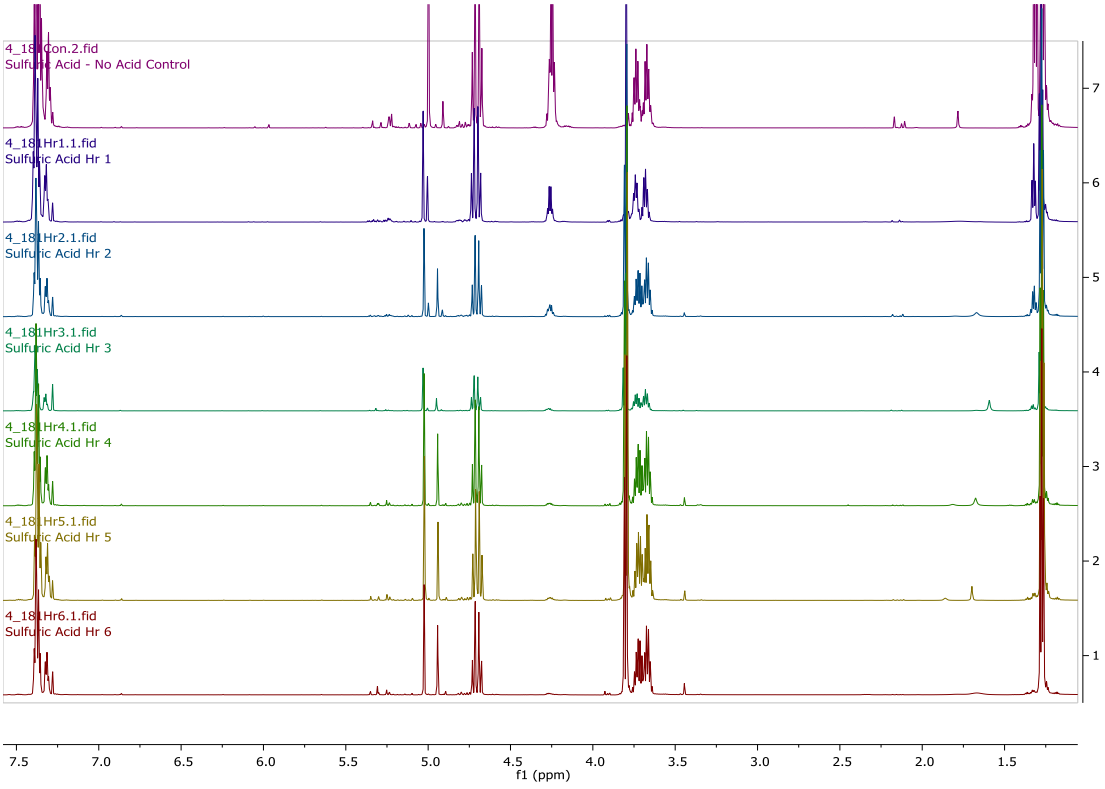
reactivity. These reactions were observed for 6 hours and compared to a standard with no acid to be sure that the compound is not inherently unstable. 1M $H_2SO_{4\ in}$ THF:H_2O and BF_3 etherate in MeOH showed no reaction after 6 hrs while 1M H_2SO_4 in MeOH simply converted the ethyl ester to a methyl ester.

Figure 56 Stability Screening






H_2SO_4 (1 eq)
MeOH


4_181Con.2.fid
Sulfuric Acid - No Acid Control
4_181Hr1.1.fid
Sulfuric Acid Hr 1
4_181Hr2.1.fid
Sulfuric Acid Hr 2
4_181Hr3.1.fid
Sulfuric Acid Hr 3
4_181Hr4.1.fid
Sulfuric Acid Hr 4
4_181Hr5.1.fid
Sulfuric Acid Hr 5
4_181Hr6.1.fid
Sulfuric Acid Hr 6
7.5
7.0
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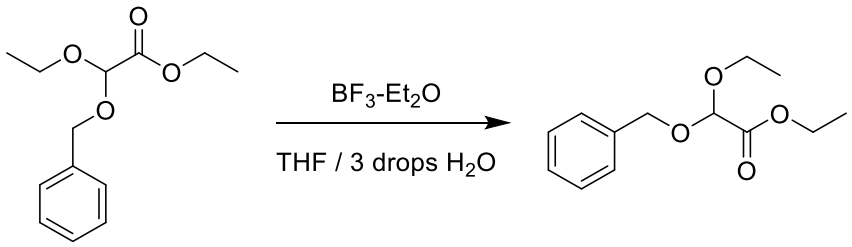
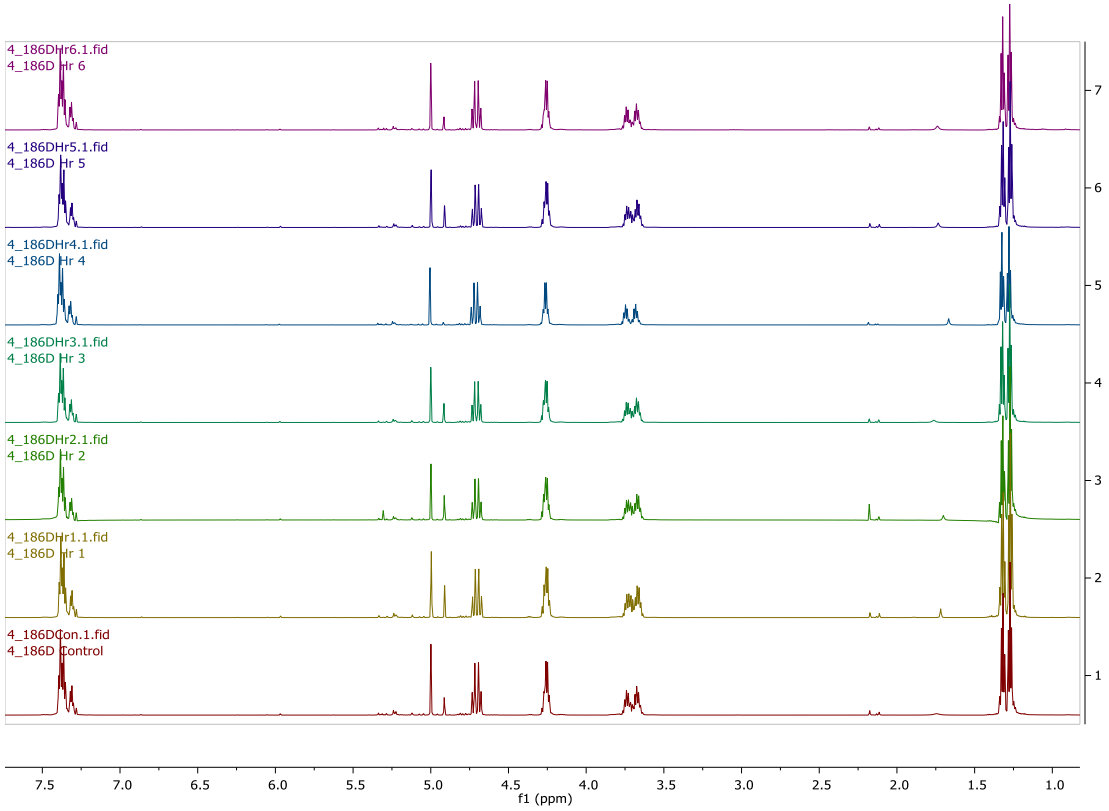
2.5
2.0
1.5
f1 (ppm)





With acid conditions proving wholly ineffectual other methods were looked into to remove the glyoxylate protecting group. The major hypothesis is that the electron withdrawing properties of the carboxylate group is preventing oxonium ion formation which is the first step in deprotection. To work around this, it was envisioned that a combination of reduction and Lewis acid might produce the desired result. Several reducing agents including $NaBH_4$, $AlBH_4$, DIBAL-H, and LAH all gave reduction but no generation of benzyl alcohol. The reduction occurs cleanly to the alcohol so further investigation into an acid treatment after reduction could prove fruitful.

Another path that was looked into was using the acetal as carbon source. Dr. Doyle has shown extensive methods to converted acetals into ethers but swapping one of the alkoxy groups with another carbon source (Figure 57).[58] Reacting a nickel catalyst with aryl borates provides di aryl ethers cleanly and efficiently. It was envisioned that this method could be applied to our glyoxylate acetal system to perform a similar reaction. A first test using Doyle's conditions proved ineffective. A full screening of conditions is likely necessary to find conditions that would be useful for this transformation.

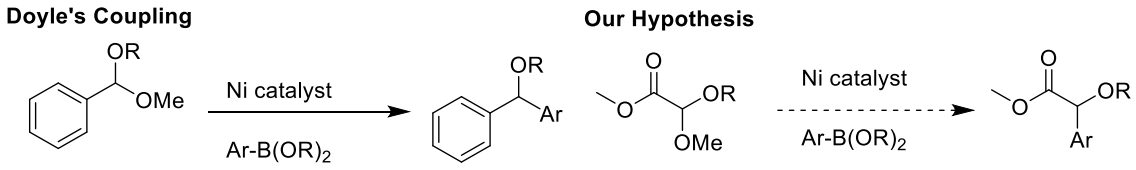


Figure 57 Application to Doyle's Chemistry

4.7 Glyoxylate Linked Glycerol Nucleosides

Moving away from the ribose-based nucleosides, there are several other backbones that have been suggested. Two of the more promising ones are GNA and isoGNA.[59,60] These DNA analogs replace the large rigid ribose backbone with glycerol. GNA links through one of the primary alcohols and the secondary alcohol of glycerol while isoGNA links through both primary alcohols. When these analogs are linked through phosphodiester linkages, both can base-pair with RNA. Since the prebiotic synthesis of ribose-based nucleosides is still a current line of investigation, these simpler systems can be a possible step along the path toward the ribonucleosides. The phosphodiester linkage for GNA/isoGNA faces the same problems as the ribonucleosides, do so replacing it with glyoxylate can serve as a prebiotic replacement for phosphodiester linkages.

Initial plans for dimerization involved first forming a cyclic glyoxylate acetal. This would be formed through standard acid catalyzed methods. From the cyclic monomer, the dimer would then be formed using the same TESOTf conditions with the ring opening

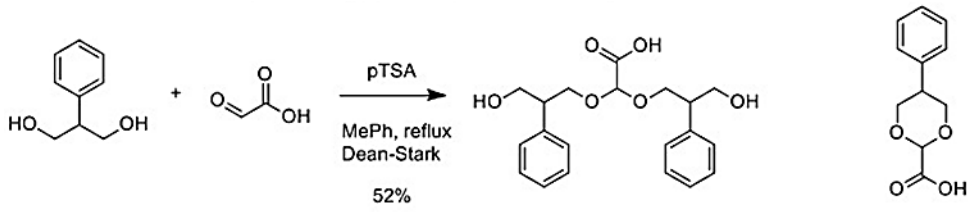


Figure 58 Model Dimerization

adding additional entropic drive for the dimerization. A model system, 2-phenyl 1,3 prop-diol, was used. Using *p*TSA, ethyl glyoxylate and a Dean-Stark apparatus we attempted to form the cyclic monomer (Figure 58). Instead what was formed was the target dimer seen. It is suspected that, in the cyclic form, the oxygen atoms are aligned to easily degrade the acetal moiety back to the oxonium ion allowing for the dimerization reaction to be the more productive pathway. The acyclic acetal is not locked into the necessary conformation to break down the acetal. Unfortunately, these conditions do not work for the GNA/isoGNA systems because those diols will not dissolve into the toluene solvent.

This result suggested another direction to move with this project. Cafferty and Hud had published results showing a new nucleobase pair, that when mixed, form six-member rosettes that stack to form long non-covalently linked polymers. [9,14] We hoped to take these bases to form isoGNA monomers then form the rosette polymers with them (Figure 59). The non-covalent polymers are assembled within a very tight pH range because a slight shift will result in structural changes that prevent assemble. 2,4,6-triaminopyrimidine and cyanuric acid assemble best at pH = 7 while barbituric acid and melamine assemble at pH = 2~3.[14] Theoretical glycol derived rosettes are seen in figure 4. We envision that the non-

covalent polymers are formed the alcohols from the glycol backbone would be positioned to react with glyoxylate included in the solution to covalently link the monomers into linear polymeric chains. The Center for Chemical Evolution is also investigating novel solvents that could assist in the replication of long polymeric chains by overcoming the strand inhibition problem. By combining our method with these deep eutectic solvents (DES)

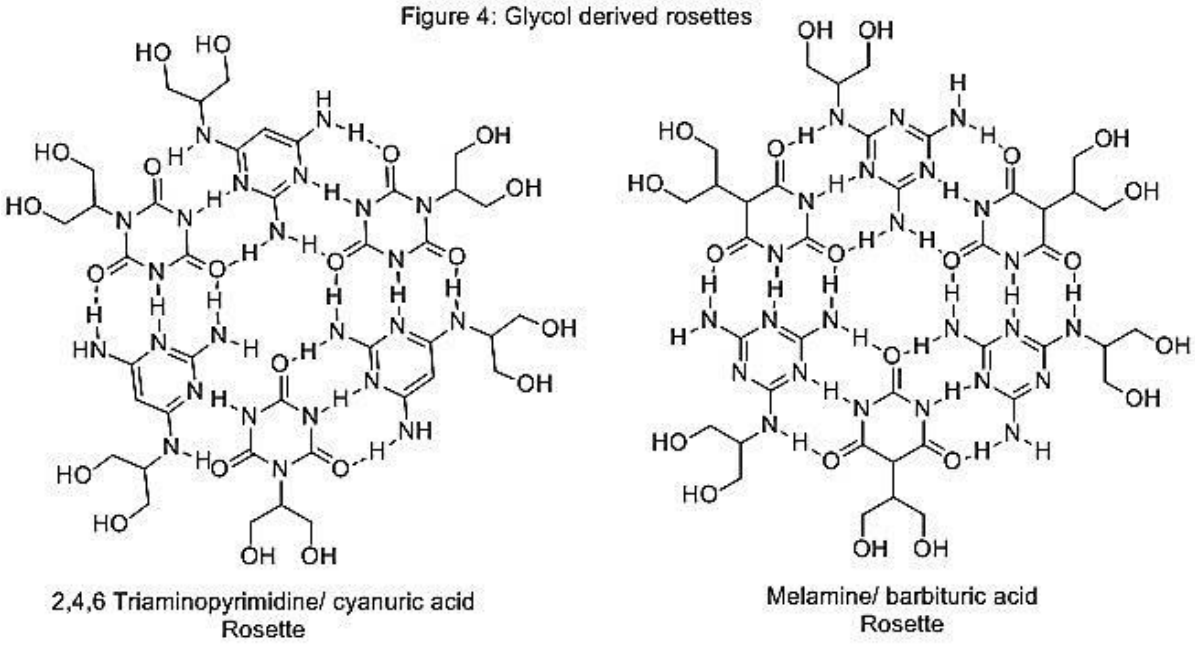


Figure 59 Rosette System with GNA

could be used to show how the first nucleobase derived polymers could have formed and self-replicated.[61] The DES prevents the long strands from diffusing as quickly as the small monomers so that the strand will not reanneal with its compliment and serve as a template for a new strand instead. The mixture would go through a cycle of pH changes that will allow for assembly then a shift in pH to melt the complex and then repeat. Since there will be no control of the sequence that is formed, it would be interesting to see if certain sequences are preferred over other ones. This would be a new view into how certain sequences may have been selected for in the early prebiotic Earth.

4.8 Synthesis of GNA and isoGNA Monomers

The synthesis of the canonical isoGNA monomers was performed following the procedure published by Dr. Krishnamurthy (Figure 60).[60] Protection of the primary alcohols followed by a Mitsunobu reaction with protected thymine provided the desired compound in good yield. Glycerol was protected with two trityl groups to give **63** while benzoylation of thymine to the protected **64** also proceeded cleanly. The Mitsunobu coupling of the two gave **65** in good yield. Finally, a two-step deprotection was achieved through treatment with methanolic ammonia to cleave the benzoyl group followed by acidification with acetic acid to provide **66** in good overall yield. The GNA-T was formed via an epoxide ring opening with thymine. The protected epoxide **67** was formed using DMTrCl which was reacted with free thymine. Using NaH, opening of the epoxide was with the proper nitrogen **68** was achieved in mild yields. Deprotection followed with TFA at nearly quantitative yield (**69**) Unfortunately, these failed to form the desired glyoxylate linkers in the same way that the nucleosides were resistant to this chemistry.

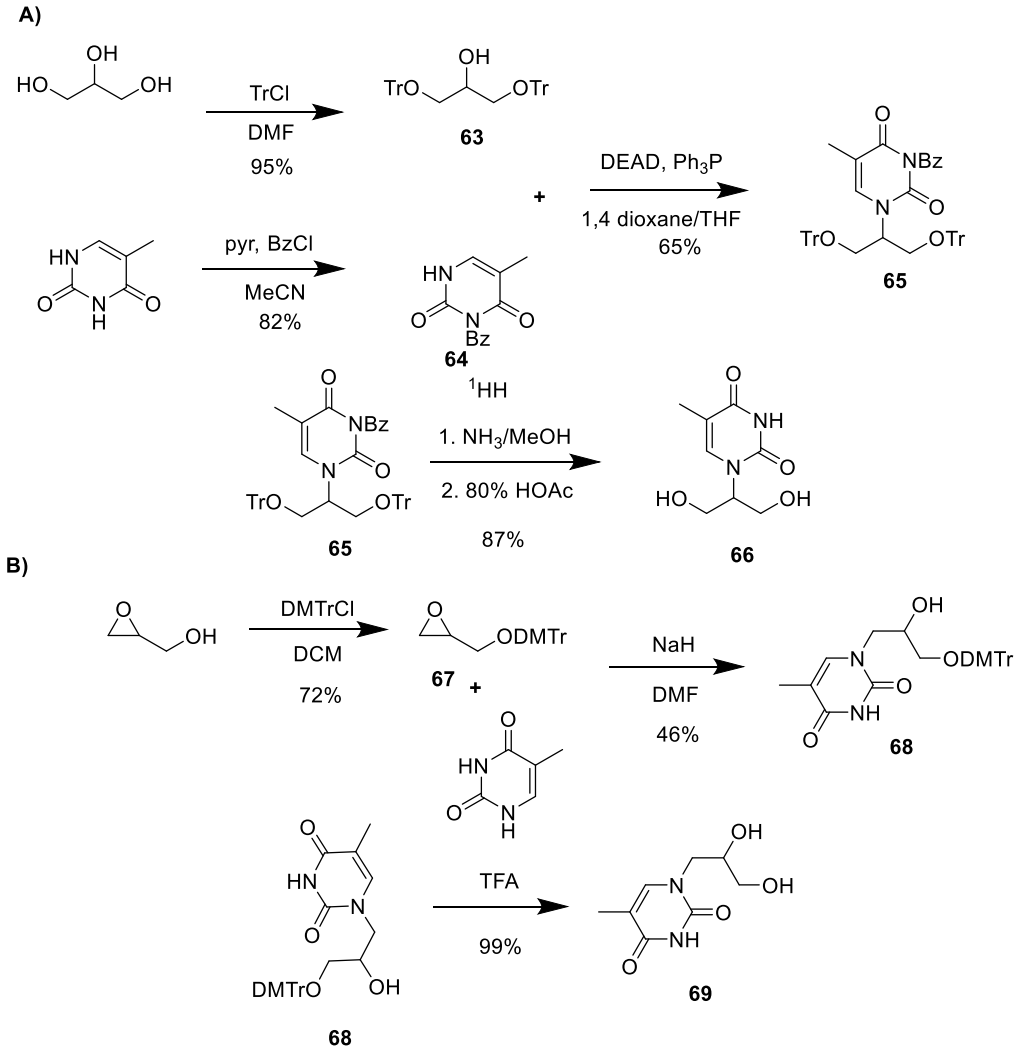


Figure 60 GNA and isoGNA Synthesis

4.9 Conclusions

This project started with idea that glyoxylate could have served as a prebiotic precursor to phosphate in the formation of DNA and RNA. There was ample evidence that both glyoxylate would be present on the early earth as well as that nucleosides such as thymidine would react to some extent to form the dimers of interest. While the dimers were observed on a small scale from dry-down experiments, this was not enough to study the system. While several years were taken to try to synthesize these systems with both

ribose and glycerol nucleoside the target system was never achieved. Acid and base mediated methods were explored in detail. Acid mediated acetalization methods seemed to be wholly ineffective as facilitating any of the desired reactivity. Conversely, base promoted methods were able to cleanly attach the first nucleoside to the glyoxylate system. Unfortunately, any attempts to finish the synthesis through either transacetalization of the mixed acetal or a second substitution reaction failed. After extensive screening of conditions and a quick test of glycerol systems which similarly proved intractable toward the transformation, the project was redirected toward the possibility of this system serving as a novel protecting group. Conditions to react a range of different alcohols were found and tested against a small collection to prove the robustness of the protection conditions. The current state of this project is trying to find the best method to remove the protecting group. The system seems to resistant to acid conditions even up to concentrated HCl. The most promising route at the moment is to combine reduction of the ester along with acid treatment of the resulting alcohol to remove the glyoxylate protecting group. After settling on deprotection conditions, a series of tests to show how orthogonal this system would be necessary. Finally, a more expansive substrate scope studying the full range of alcohols that are conducive to this type to chemistry is likely also needed to publish. This would be a novel method and orthogonal to many current alcohol protecting groups. Being stable to both acid and base is a major advantage of this system. Strong reducing conditions would be an issue for late stage natural product deprotection as most targets possess a reducible functionality. The full breadth of this project has moved a large distance from where it started.

What began as a simple synthesis of a prebiotic DNA/RNA analogs to study their base-pairing properties lead to a full analysis of the chemistry of nucleosides. When it became apparent that no progress was being made after many attempts to overcome the problems a way to salvage something was analyzed. The stability of the acetal directed the thinking toward the possibility of a novel alcohol protecting group. Some progress has been made though the majority of the time was directed toward other projects that the Center viewed as being more interesting and in tune with the current work there. Recently, this has been returned to in the hopes of being able to determine the best deprotection conditions.

CHAPTER 5: KETO-ACID SUGAR AS PREBIOTIC LINKER

This chapter presents a separate attempt to overcome the intransigence of forming glyoxylate-linked nucleosides. The envisioned model has the glyoxylate tethered to the nucleoside through a 4-carbon chain that would cyclize to form a bicyclic system. This could self-polymerize more easily than nucleosides and glyoxylate. The synthesis of the system proved highly difficult with several unexpected roadblocks. The problems and methods to overcome them along with the current state of the project is shown.

5.1 Introduction

In the continuing effort to determine a plausible pathway to form RNA and RNA like proto-biopolymers, linking monomers together via a small molecule linker is a major hurdle. Bringing together both the monomers and whatever small molecule is envisioned as a linkage between them has serious kinetic and steric issues.[62,63] Biology overcomes this issue with a combination of finely designed enzymes and activated monomers.[64] Glyoxylate and pyruvate were viewed as possibly overcoming this because the acetal linkage is more thermodynamically possible than the phosphorylation under prebiotic conditions.[65] In Chapter 4, we found that even with that, the entropic resistance to bring two large nucleosides together around a small molecule without some way to activate the system is prohibitively difficult.

The next question is whether this 10-carbon linear sugar acid is a plausible product of prebiotic reactions. The Center has spent a great deal of time looking at pathways by which linear sugars and sugar acids could be formed. The formose reaction, which for a long time, was consensus opinion on how sugars were generated on the early earth. From this reaction not only are the linear sugars but also a large number of branched sugars are

observed and this extremely messiness has been a problem in the literature. One of the compounds of particular interest in the Center has been glyoxylate which has been seen in a wide range of differing chemistry. In this context, reactions between glycolaldehyde and glyoxylate lead to an iterative glyoxylate addition followed by decarboxylation shown below that will selectively generate linear sugar acids.

Looking into the long keto-acid sugars that have been shown to be formed under prebiotic conditions by the Krishnamurthy laboratory[66], we envisioned a possible pathway that could lead directly to a possible precursor to RNA (Figure 61). Through a 10-carbon keto-acid sugar we suggest that this type of linear sugar could cyclize as shown to form a bicyclic structure. The bicyclic structure possesses both a ribose portion and a pyranose portion. The ribose half is primed for nucleosidation, especially by various non-canonical nucleobases of the type that are being studied in Dr. Hud's Lab (Figure 62).[67] Through the pyranose half the monomer can self-polymerize, through the hemiacetal moiety present in the monomer, to form a proto-RNA polymer without the need for an additional molecule to serve as the linker. The tethered carboxylic acid will act as a phosphate surrogate, providing the negative charge to facilitate the formation of the RNA-like duplexes.[51] This has the possibility to provide a mechanism through which disparate nucleosides assembled in non-covalently linked assemblies can interconnect to form a covalent polymer without adding an additional molecule to connect each monomer.

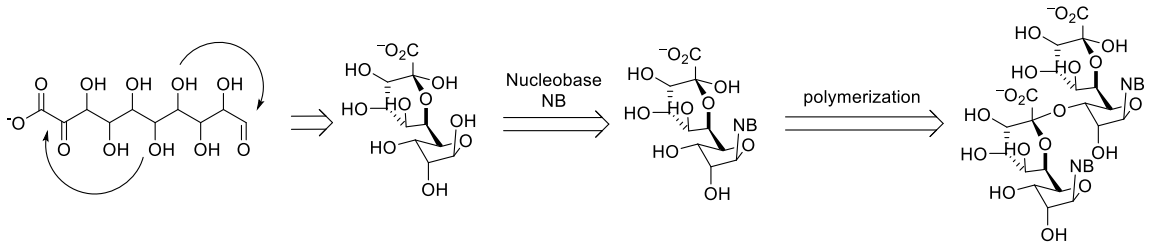


Figure 61 Hypothesized Keto-Acid Bicycle

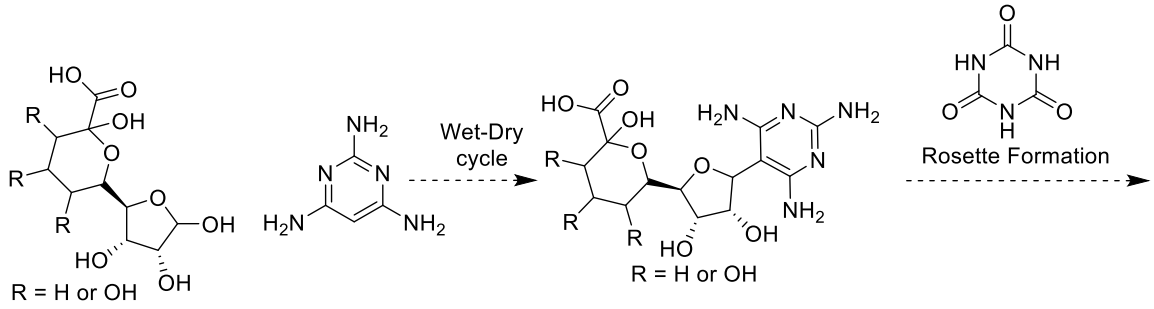


Figure 62 Rosette Formation with Keto-Acid Sugars

Another advantage with this hypothesized monomer is that while there are two anomeric centers they each have distinct chemical environments that would serve to allow selectivity in reactivity. Nucleosidation of sugars has been shown to be selective for electron-rich anomeric centers. The adjacent carboxylic acid would cause the anomeric center on the pyranose ring to be significantly less reactive toward nucleosidation. With this selectivity we hoped that a reaction of this system with a nucleobase would generate the nucleoside monomer which could then be polymerized or dimerized to study its interaction with DNA and RNA to determine the possibility of this molecule could serve as an intermediate in the evolution toward these extant macromolecules.

The center had also shown that nucleosidation of ribose with alternative nucleoside such as TAP and cyanuric acid is much more favorable in prebiotic conditions.[9,14] One of

the current drawbacks of the TAP/CA system is the fact that while these nucleobases are able to assemble into interesting rosette columns, they are totally non-covalently linked. This means that if it were envisioned as a proto-DNA informational system it currently could not retain information. This bicyclic system could serve to overcome this problem. TAP/CA have already been shown to cleanly nucleosidase ribose suggesting that they should react similarly with the hypothesized system. Simple wet-dry cycling would provide the nucleosidated system and reactivity should be restricted to the ribose ring as that portion is more reactive than the pyran ring with a pendant electron withdrawing carboxylic acid moiety adjacent to it. The pyran ring would be held in a position close enough to the next layer of the rosette assembly to encourage polymerization. There are hopes that these compounds could be used with our hypothesized bicyclic linker to form interesting systems. Before targeting the fully hydroxylated and prebiotic monomer, a similar alkane linkage was viewed as a positive first step in this project.

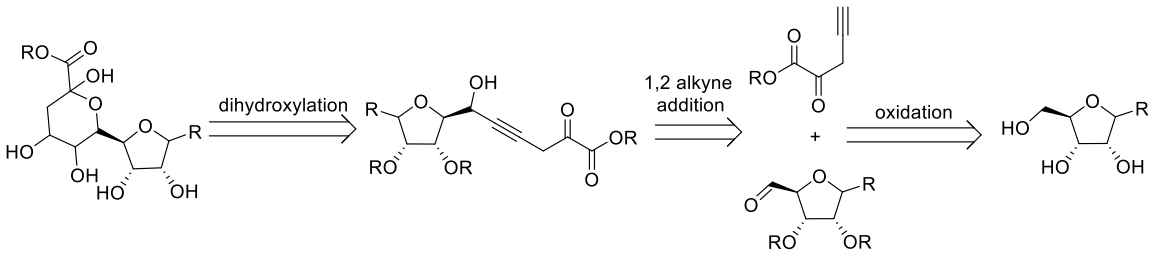


Figure 63 Retrosynthetic Analysis of Bicyclic Keto-Acid Sugar

Our retrosynthetic analysis of this target followed a convergent approach (Figure 63). The ribose/nucleoside half will be converted to an aldehyde which after reaction with a terminal alkyne that forms the tether, will generate the desired carbon skeleton. Hydrogenation of the alkyne and deprotection of the ketone should then provide the target in a quick and efficient manner.

5.2 Model System

Initial goal of this project was to generate a model system with an aryl ring in place the ribose. This model allows for the determination of whether the pyranose form would spontaneously form with an α-keto acid on the end of the tether (Figure 64). To access this species, we generated the terminal alkyne **71** from the reaction of *di*-thiethoxy ethyl acetate **70** with propargyl bromide which proceeded in moderate yield. This alkyne was deprotonated with nBuLi and reacted with benzaldehyde to form full carbon system seen in **72**. Hydrogenation occurred very poorly, providing only ~6% yield of **73** likely from some poisoning of the palladium catalyst by the thiane. Even with that, enough was generated to see formation of the pyranose ring. With this positive result we set forth to generate the similar compound with a nucleoside or ribose.

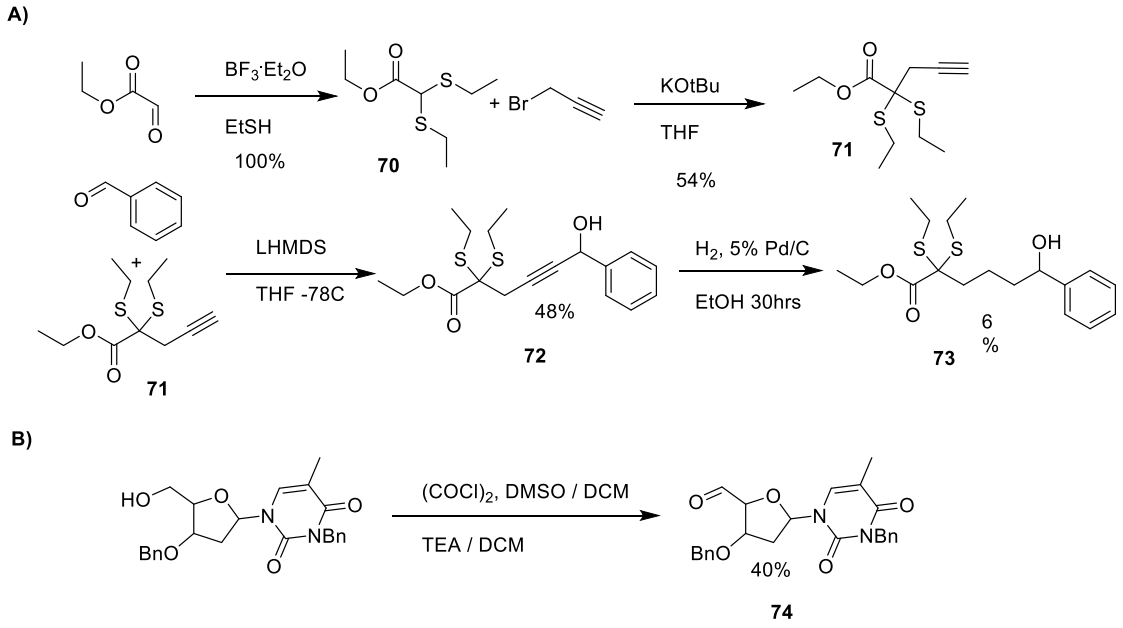
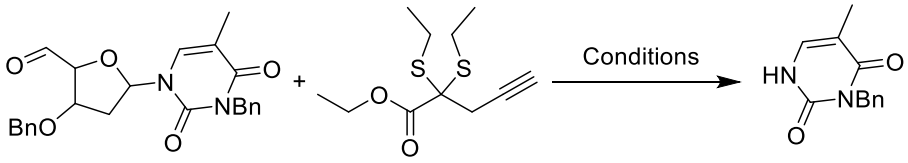


Figure 64 A) Model System Synthesis B) Oxidation of Protected Thymidine

5.3 Thymidine Tests

The first ribose/nucleoside substrate that was used was the thymidine derivatives that were used throughout the first set of studies into glyoxylate acetals (Table 7). The debenzylated thymidine was oxidized selectively to the aldehyde **74** via a Swern oxidation. Since the thiane alkyne was able to react cleanly with benzaldehyde it was suspected that this similar system should be amenable with thymidine.

Table 7 Thymidine Aldehyde Tests



Conditions	Result
LHMDS, THF -78°C	Thymine
LHMDS, THF -78°C (propargyl bromide)	Thymine
LHMDS, THF -78°C (dropwise)	Thymine
NaHMDS, THF -78°C	Thymine
KHMDS, THF-78°C	Thymine
MeLi, CuI, THF -78°C	Baseline
iPrMgBr, THF -78°C	Thymine
$ZnOTf_2$, TEA, MePh, rt	Thymine

A range of different conditions were attempted to facilitate the aldol addition. Various HMDS bases as well as Grignards and even a weak base like TEA were all attempted but all resulted in total denucleosidation of the thymidine. This was a particularly surprising result as nothing had been seen in the literature suggesting that nucleosides would have this kind of reaction with bases. The only condition that did not result in denucleosidation was MeLi and CuI but instead of giving the desired aldol product only baseline degradation was observed. Adenosine (Figure 65A) was also tested but still resulted in denucleosidation. Control reactions (B&C) showed that the alkyne was not

necessary to result in denucleosidation as simply stirring the aldehyde in LHMDS facilitated the reactivity. Interestingly the alcohol was totally stable to the conditions. This suggests that likely deprotonation α to the aldehyde likely is what initiates the reactivity.

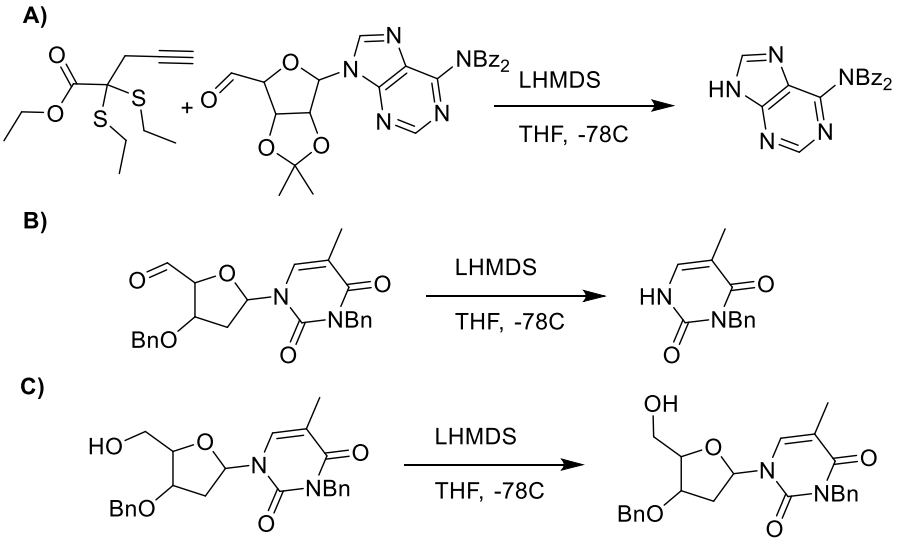


Figure 65 Denucleosidation Test Reactions

Before moving toward other substrates to solve the aldol issue, the model system was returned to as a way to test if the pyranose ring will be able to be opened easily to form the desired linkage (Figure 66). The hydrogenation of the internal alkyne that was synthesized previously was found to be low yielding for the alkane **73** using palladium but with platinum the *Z*-alkene **74** was formed at ~42% yield but was used crude for the next step. Treatment of the alkene with silver triflate gave the unsaturated pyranose **75** in 60% yield.

5.4 Model Cyclization and Attempted Coupling

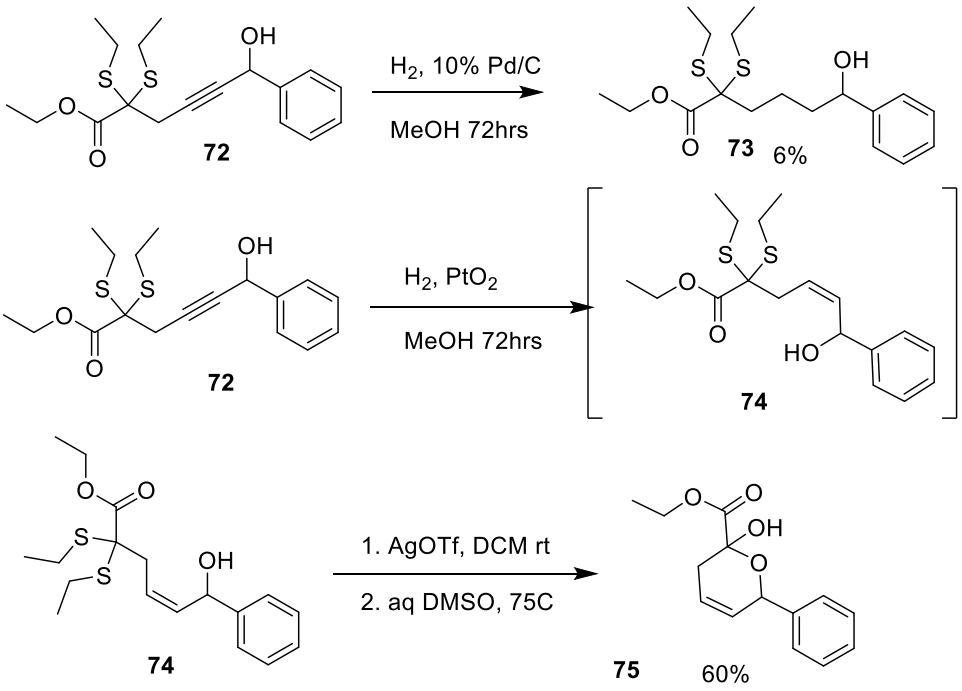
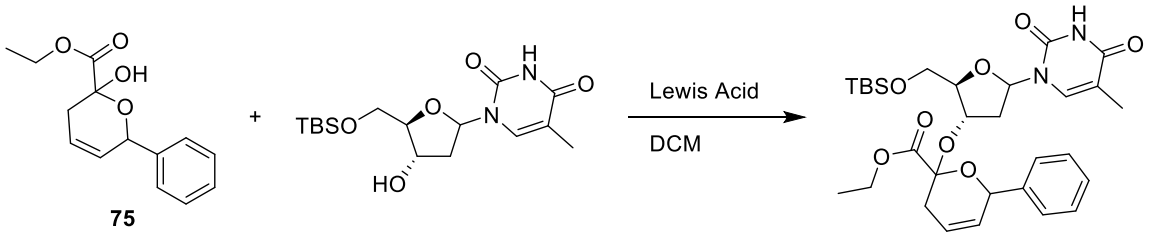


Figure 66 Model Hydrogenation

With the model pyranose in hand a series of tests were performed to determine if conversion of the hemi-acetal to an acetal with a 3' nucleoside forming the analog to the hypothesized linkage that could have existed in the prebiotic system. A range of different protic and Lewis acids were tested but all failed to give the desired product except for pTSA which gave a trace amount but increasing loading or equivalences failed to result in an isolatable amount of material (Table 8).

Table 8 Transacetalization of Model System Tests



75

Lewis Acid	Loading	Time	Result
$SnCl_4$	100%	12 hrs	Decomposition
pTSA	100%	24 hrs	Trace <5%
BF_3Et_2O	100%	24 hrs	5' deprotection
TMSOTf	100%	6 hrs	Decomposition
$HfOTf_4$	100%	24 hrs	5' deprotection
MgCl (drydown)	100%	3 days	No Reaction

5.5 Ribose System

With the extreme difficulty exhibited by the nucleoside systems it was decided to try ribose as an alternative starting point for the synthesis. There were several things that may make ribose a good substrate. The lack of a nucleobase, obviously, makes that particular path of degradation impossible so it was hoped that that would make it more stable and easier to build the rest of the carbon chain onto it. Also, some previous studies in the center showed that ribose would react well with alternative nucleobases such as triaminopyrimidine and cyanuric acid. This would be very interesting as the bicyclic monomer that is formed should possess the ability to form the large noncovalently linked rosette stacks that TAP and CA form. Following this, the monomers may be able to covalently link together and exhibit proto-DNA like properties.

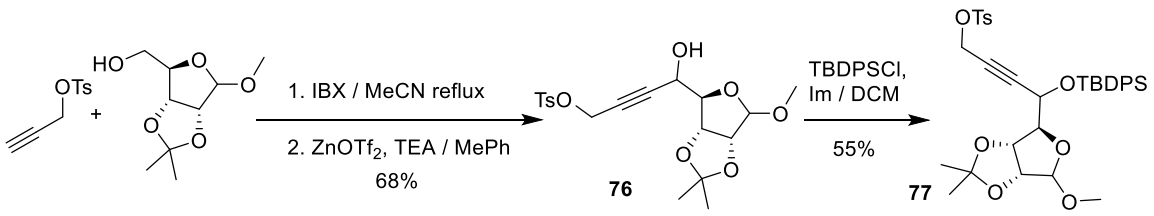
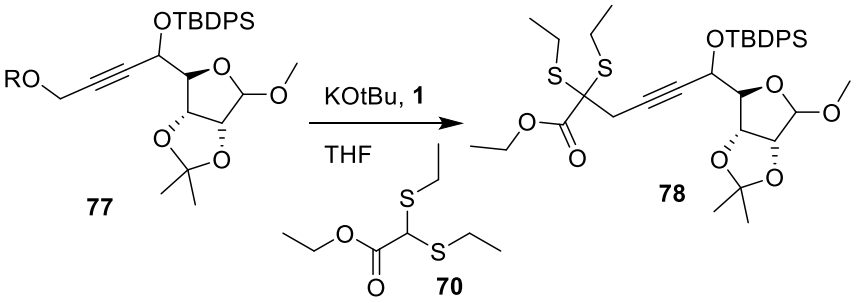


Figure 67 Synthesis of Ribose System

Formation of the ribose substrate utilized a modification of previously published literature (Figure 67). The protect OMe-ribose acetonide was oxidized with IBX and reacted with propargyl alcohol in the presence of TEA and zinc triflate to form the internal alkyne. A global protection using TBDPSCl gave the disilylated product in 55% yield. Selective deprotection of the primary alcohol via a single equivalent of TBAF followed by conversion to various sulfones returned the synthesis to the final addition of glyoxylate thiane to form the full carbon skeleton. Unfortunately, all of the sulfones had differing issues (Table 9). The triflate and nosylate both decomposed under the reaction conditions. Tosylate and mesylate at room temperature gave very low yields. Refluxing the tosylate gave approximately 40% yield but the thiane was running alongside of the product and all attempts to remove it failed.

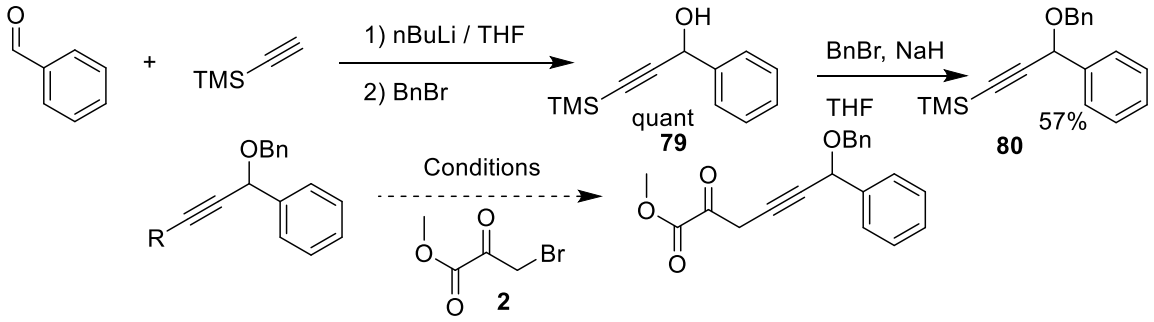
Table 9 Thiane Substitution Test Reactions



R =	Temp	Time (hrs)	Yield / Result
Ts	Rt	16	10%
Tf	Rt	5	Decomposed
Ms	Rt	16	10%
Ns	Rt	6	Decomposed
Ts	Reflux	20	40%* (2:1) (**1:2**)

With the bases seeming to be an issue the model was returned to determine if using TMS acetylene with bromopyruvate to be able to form the carbon skeleton (Table 10). Unfortunately, in all cases either desilylation or addition to the carbonyl were observed.

Table 10 Fluoride Initiated Bromo-pyruvate Substitutions



R =	Conditions	Result	Yield
TMS	TBAF	Desilylation	99%
TMS	CsF	No Reaction	
TMS	TBAF (slow add)	Desilylation	95%
TMS	TASF	Desilylation	95%
H	LHMDS	Carbonyl Addition	61%

Finally, a method to form the carbon skeleton was found by way of an epoxide ring opening but attempts to oxide the homopropargyl alcohol (Swern, IBX, DMP and PDC) all failed, giving decomposition products (Figure 68).

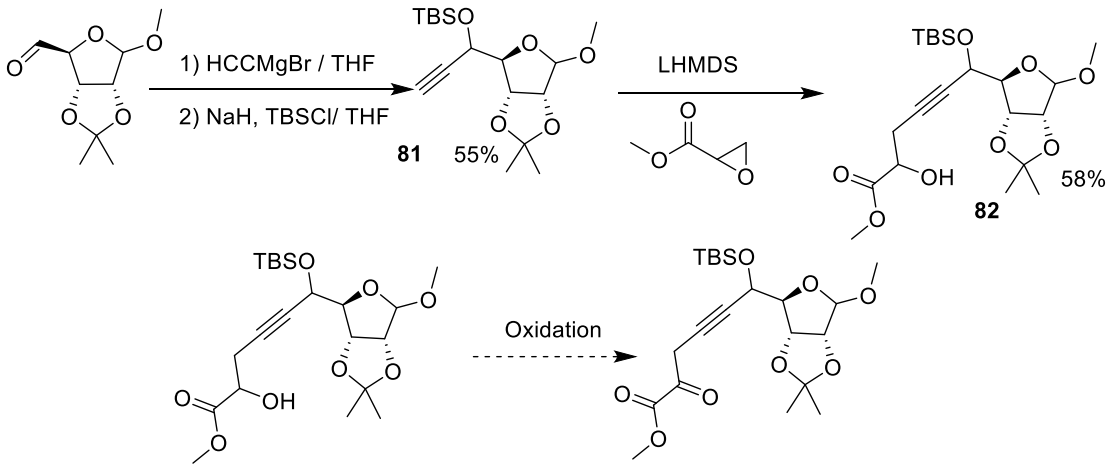


Figure 68 Oxidation Attempts

5.6 Conclusions

This project has had a series of difficult setbacks to it. Initial attempts to form the nucleoside bicyclic product failed in all cases. A totally unexpected denucleosidation occurred when attempting to perform an aldol addition to the 5' aldehyde. After extensive testing it was determined that this was an intrinsic property of the 5' aldehyde nucleosides. The mechanism for the is decomposition is still unknown though the dependence on the presence of a base suggests that deprotonation adjacent to the aldehyde is likely a key step in the process. Shifting to ribose allowed for a further advance in the synthesis. After finding the proper way to form the full carbon skeleton through an alkyne epoxide ring opening. The current hold of the synthesis is the difficulty in performing the oxidation of the alcohol a ketone. This would allow for cyclization and hopefully complete the synthesis after deprotection and hydrogenation of the alkyne to allow for flexibility in the carbon chain. Unfortunately, the alcohol proved to be totally resistant to oxidation regardless of conditions used. It is uncertain as to whether a set of conditions could be found to successfully complete this synthesis. Work in the center moved away from this

line of work as new methods of sugar and oligosaccharide formation were investigated. Also, the idea of using this type of linkage with the non-canonical nucleobases was decided to be unfruitful both with the difficulty of synthesis and questions regarding the possibility of its existing prebiotically.

CHAPTER 6: SUMMARY AND OUTLOOK

6.1 Summary

Throughout this work, glyoxylate has had a central location. Along with DHF, glyoxylate has served both as substrate for novel methodologies as well as building block for synthesizing larger complex systems. All of these different projects were focused on a central focus, applying synthetic organic chemistry knowledge to solve and advance origin of life questions. The new chemistries that had been only of interest to those in the origin of life field have started to be expanded into the organic synthetic realm. DHF has been shown to be a useful methodological unit to perform formal glycolaldehyde aldol additions without the need for protecting groups. Glyoxylate was used to try to form prebiotic nucleic acid systems. While these attempts failed a new and interesting alcohol protecting group was developed from the failures.

DHF proved to be the most successful thrust of this research in Chapters 2 and 3. The nucleophilic chemistry of DHF was first fleshed out within the CCE and found that depending on the pH of the aqueous solution differing product distributions were observed. Tartrate was seen when reacted with glyoxylate at high pH while at near neutral pH sugars and sugar acids were seen instead. After significant experimentation both types of products were able to be formed with a range of different aldehydes.

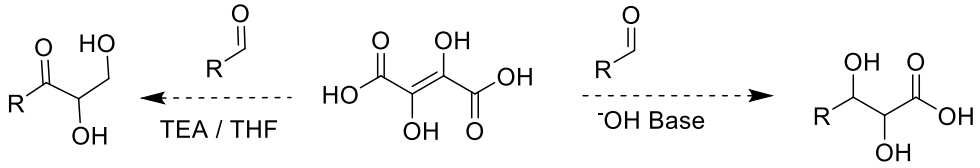


Figure 69 DHF Overview

It was determined that when a weak base, TEA, was used at high temperatures a decarboxylative mechanism dominates while with stronger bases, NaOH and LiOH, at

cooler temperatures a deoxalative mechanism dominates. The fundamental properties of DHF were also explored and found that changing the natural of the carboxylic acid moiety resulted in major changes to reactivity (Figure 69).

One of the substrates used for the decarboxylative study was vanillin. This successfully synthesized the natural product *C*-veratroylglycol. With this in hand a new project was initiated interested in applying this method to the synthesis of other lignan and neolignan natural products. Significant progress has been made on these targets with only unifying the two parts of each remaining. Hopefully at least the first few targets could be made in a matter of weeks if the final chemistries are amenable to the substrates. If this can be achieved this new method would be extremely useful toward the synthesis of lignan derived natural products. Being able to start from the aldehyde and form the dihydroxy chain in a single un protected step could be powerful.

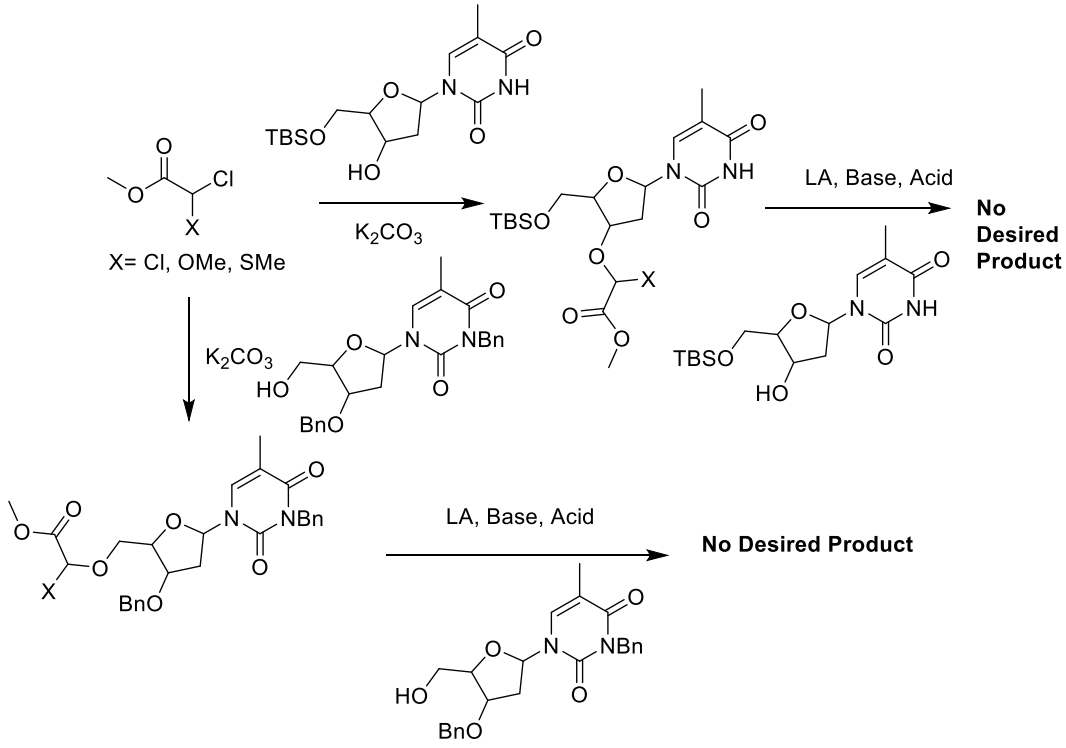


Figure 70 Glyoxylate Summary

Glyoxylate was at first studied as a prebiotic precursor for phosphate in Chapter 4 (Figure 70). There was an expectation that if combined with nucleosides a prebiotic precursor to DNA would be formed and studied. Through a wide selection of differing methods, the linkage was attempted to be made. Unfortunately, these attempts proved to be ineffective in achieving what was desired. It was decided that the impressive resistance to reactivity of the glyoxylate acetals would be applied to developing a novel protecting group for alcohols. Significant progress has been made to this end with a strong and robust method of attaching the protecting group already in hand. To complete the progress on this project deprotection conditions and proof of orthogonality are still required. A combination of reducing and acidic conditions is likely necessary to achieve this desired effect. If these steps can be achieved then this has the possibility of resulting in a publication though significant time may be required depending on how quickly the deprotection conditions can be determined.

The last thrust of this work, in Chapter 5, focused on trying to synthesize a 10-carbon keto-acid sugar. The target was initially of interest as it was hypothesized to act as a way to link together nucleosides in a proto-DNA system. Starting methods of synthesis for these nucleoside bicycles utilized a nucleoside as starting point with the plan of building the pyran ring onto the already formed system. An unexpected issue was found in the form of a denucleosidation problem when reacting the nucleoside aldehyde. Because of this there was a shift to simply synthesizing the keto-acid sugar as a proof and test of complex organic synthesis. More progress was made on that route and several roadblocks were worked around but finally were stopped on the oxidation of a homopropargylic alcohol to form the α-keto acid. Attempts to work around this issue all failed. This project could be

close to being done if a method to perform the oxidation is found though if that proves totally resistant to the chemistry then a return to the drawing board is likely necessary.

All told, this work has expanded the understanding that certain ideas and hypotheses might seem possible and straightforward when envisioned on the early earth they may not be so simple to prove or even make to be able to test. Throughout the span of these projects both the prebiotic synthesis and synthetic organic synthesis of a range of different compounds were attempted along with novel prebiotic reactions being converted into synthetically useful organic methodologies. These discoveries have directed work in the CCE toward more promising paths by finding that certain hypothesized compounds are much harder to make than previously thought alongside proved the applicability of prebiotic chemistry discovered in the center to fields beyond origin of life.

APPENDIX: EXPERIMENTAL

General Information

Chromatographic purification was performed as flash chromatography with Silicycle SiliaFlash P60 silica gel (40–63 μm) or preparative thin-layer chromatography (prep-TLC) using silica gel F254 (1000 μm) plates and solvents indicated as eluent with 0.1–0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Silicycle SiliaPlate TLC silica gel F254 (250 μm) TLC glass plates. Proton and carbon nuclear magnetic resonance spectra (1H NMR and 13C NMR) were recorded on a Bruker 500 MHz or 700MHz spectrometer with solvent resonances as the internal standard (1H NMR: CDCl3 at 7.28 ppm; 13C NMR: CDCl3 at 77.0 ppm). 1H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. MestraNova was used to analyze NMR spectra. Infrared Spectra were obtained on a Thermo Nicolet 6700 FTIR and analyzed using OMNIC software. IR data is reported as follows: peak (cm-1) and intensity (s = strong, m = medium, w = weak, br = broad). Mass spectra were obtained through EI on a Micromass AutoSpec machine or through ESI on a Thermo Orbitrap XL. The accurate mass analyses run in EI mode were at a mass resolution of 10,000 and were calibrated using PFK (perfluorokerosene) as an internal standard. The accurate mass analyses run in EI mode were at a mass resolution of 30,000 using the calibration mixture supplied by Thermo. DFT calculations performed using B3LYP functional with 6-31G* in the gas phase as the basis set.

Dihydroxy Fumaric Acid Experimental Procedures

*Synthesis of DiMeDHF **2***

In a flame dried flask, DHF hydrate (5g, 27.2mmol) was dissolved in 35mL of anhydrous MeOH (1M) under an inert atmosphere. The resulting solution was cooled to 0°C and 2.2 eq of thionyl chloride (8.8g, 59.7 mmol) was added. The reaction was warmed to room temperature and stirred for 2 days while a white precipitate was formed. The precipitate was recovered by filtration to provide 4.4g of pure DiMeDHF (74%). Characterization matches previously published results.[68]

Reactions of DiMeDHF

Base-Free reactions of DiMeDHF- In an argon charged flame dried flask, 150mg (0.8 mmol) of DiMeDHF was added to 5mL of THF or $CDCl_3$. Added to this mixture, 1 eq of benzaldehyde (90.4mg, 0.8 mmol) or 4-nitro benzaldehyde (128.7mg, 0.8 mmol) followed by refluxing in the appropriate solvent. Progress was monitored by TLC and crude NMR but no reaction observed after 24 hrs. After cooling, the DiMeDHF was completely recovered.

TEA reaction of DiMeDHF - In an argon charged flame dried flask, 150mg (0.8 mmol) of DiMeDHF was added to 8mL of THF. 1 eq of benzaldehyde (90.4mg, 0.8 mmol) and 3 eq of triethylamine (242.9mg, 2.4 mmol) were added to the reaction and stirred at reflux for 24 hrs. The reaction was quenched with water and extracted into EtOAc. An unknown product was isolated from the organic phase. Analysis of the NMR was inconclusive regarding whether it is Cannizzaro or some other reactivity.

Room temp reaction – In an argon charged flame dried flask, 150mg (0.8 mmol) of DHF hydrate was dissolved in THF-d_8 with 1 eq of benzaldehyde (90.4mg, 0.8 mmol). Reaction

was stirred for 24 hrs at room temperature. The reaction was monitored by NMR and TLC but no new products observed by TLC

DHF Derivative Self-Reactivity Studies

To determine the relative stability of DHF and DiMeDHF, 150mg of both were dissolved in refluxing THF (7 mL) for 3 days. At which point the reactions were cooled to room temperature and concentrated to dryness. The crude mixture was then analyzed by NMR. DiMeDHF was completely recovered while only 10% of DHF had reacted to give pentulosonic acid and other side products. The Di-lithiated DHF stability was confirmed by using the previously published self-reactivity of DHF by Sagi *et al.*[69]

Deconvolution of Deoxalation and Self Condensation Pathways

Using standard deoxalation conditions, 150 mg (0.814mmol) of DHF and benzaldehyde **8a** (259 mg, 2.44 mmol), NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol). After acidification by Amberlyst A-15 resin, the crude aqueous residue was analyzed by 2D NMR.

DHF Fragmentation Control & Spiking

Using a variation standard deoxalation conditions, 150 mg (0.814mmol) of DHF was dissolved in 7mL of distilled water. 4 eq (0.130mg, 3.26mmol) of NaOH and 2 eq (0.068mg, 1.68mmol) of LiOH hydrate were added and the reaction was stirred for 18hrs at room temperature. At which point, Amberlyst A-15 resin was added until the pH of the solution was ~4. The resin was then filtered off using a Buchner funnel and rotovapped to dryness at ~70°C. The residue was then analyzed by NMR. *D, L* tartaric acid (5 mg) was added to the NMR sample to determine the location of the tartrate peaks. *meso*-Tartaric acid was determined by comparison to known literature. Pure glycolic acid (5 mg) was

added to the tartaric acid NMR sample to confirm its location and tartronic acid was assigned by comparison to previously published results.

3.2. *General Procedure for Synthesis of (Hetero)aryl 2,3propionones (10)*

A dry round-bottom flask was charged with a stir-bar, and DHF dihydrate (1 equiv) was added, followed by freshly distilled solvent. The respective aldehyde **7** or **13** (3 equiv) was added followed immediately by the addition of triethylamine (3 or 4 equiv). A reflux condenser was attached to the flask and the reaction was heated at reflux. As determined by TLC, after 18 h, the reaction was diluted with CH_2Cl_2, concentrated under reduced pressure, and purified by flash column chromatography on silica gel using EtOAc/Hexanes as the mobile phase.

2,3-Dihydroxy-1-phenylpropan-1-one (**10a**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), benzaldehyde **7a** (173 mg, 1.63 mmol), triethylamine (220 mg, 2.17mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10a** was afforded as a pale-yellow oil (65 mg, 72% yield). Characterizations were consistent with previously reported literature.[70]

2,3-Dihydroxy-1-(p-tolyl)propan-1-one (**10c**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-tolualdehyde **7c** (196 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10c** was afforded as a pale-yellow oil (53 mg, 54% yield). **^{1}H NMR** (501 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.16 (dd, *J* = 5.1 Hz, 3.3 Hz, 1H), 4.03 (dd, *J* = 11.7 Hz, 3.3 Hz, 1H), 3.75 (dd, *J* = 11.7 Hz, 5.1 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ =

198.8, 145.5, 130.8, 129.7, 128.7, 74.3, 65.5, 29.7. **IR** 3434 (m), 3394 (m), 2940 (w), 1680 (s), 1595 (s), 1503 (w) cm^{-1}. **HRMS** ESI m/z [MNa^+] Calcd. for $C_9H_{12}O_3Na$ 203.0679; Found 203.0678.

1-(4-Ethylphenyl)-2,3-dihydroxypropan-1-one (**10d**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-ethylbenzaldehyde **7d** (219 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10d** was afforded as a pale-yellow oil (43 mg, 41% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 5.14 (td, *J* = 5.1 Hz, 3.2 Hz, 1H), 4.04 (d, *J* = 5.7 Hz, 1H), 4.01 (d, *J* = 12.2 Hz, 1H), 3.73 (d, *J* = 10.1 Hz, 1H), 2.72 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 1H), 1.26 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 198.8, 151.6, 130.9, 128.8, 128.7, 128.5, 126.9, 74.4, 65.5, 29.0, 15.1. **IR** 3348 (br), 2962 (m), 2928 (m), 2870 (w), 1675 (s), 1606 (w) cm^{-1}. **HRMS** (ESI) m/z: [MNa^+] Calcd. For $C_{11}H_{14}O_3Na$ 217.0835; Found 217.0834.

2,3-Dihydroxy-1-(4-isopropylphenyl)propan-1-one (**10e)**

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-ethylbenzaldehyde **7e** (241 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10e** was afforded as a pale-yellow wax (16 mg, 14% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.14 (t, *J* = 4.2 Hz, 1H), 4.06 (s, 1H), 4.02 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.74 (dd, *J* = 11.8, 5.2 Hz, 1H), 2.98 (hept, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 6H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 198.8, 156.2, 131.1, 128.9, 127.4, 127.1, 126.9,

74.4, 65.5, 34.4, 23.6. **IR:** 3401 (br), 2960 (s), 2925 (s), 1678 (s), 1606 (w) cm^{-1}. **HRMS** (ESI) m/z: [MNa^+] Calcd. For $C_{12}H_{16}O_3Na$ 231.0992; Found 231.0993.

1-(4-Fluorophenyl)-2,3-dihydroxypropan-1-one (**10f**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-fluorobenzaldehyde **7l** (202 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **1l** was afforded as a colorless oil (65 mg, 65% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.9 Hz, 5.3 Hz, 2H), 7.22 (dd, *J* = 8.9 Hz, 8.3 Hz, 2H), 5.15 (q, *J* = 4.5 Hz, 4.0 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 4.00 (d, *J* = 5.8 Hz, 1H), 3.78 (d, *J* = 8.6 Hz, 1H), 2.25 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 197.8, 166.4 (d,

J = 257.1 Hz), 131.3 (d, *J* = 9.5 Hz), 129.3 (d, *J* = 3.4 Hz), 116.3 (*d*, *J* = 22.1 Hz), 74.4, 65.3 ppm **IR**: 3340 (s), 2911 (w), 1679 (s), 1597 (s), 1507 (m) cm^{-1}. **HRMS** (ESI) m/z: [MH^+] Calcd. for $C_9H_{10}O_3F$ 185.0608; Found 185.0606.

1-(3-Fluorophenyl)-2,3-dihydroxypropan-1-one (**10g**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 3-fluorobenzaldehyde **7g** (202 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.25), compound **10g** was afforded as a pale-yellow oil (31 mg, 31% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ = 7.72 (dt, *J* = 7.7 Hz, 1.2 Hz, 1H), 7.65 (ddd, *J* = 9.1 Hz, 2.5 Hz, 1.6 Hz, 1H), 7.52 (td, *J* = 8.0 Hz, 5.4 Hz, 1H), 7.37 (tdd, *J* = 8.2 Hz, 2.6 Hz, 1.2 Hz, 1H), 5.14 (t, *J* = 3.8 Hz, 1H), 4.04 (q, *J* = 5.0 Hz, 1H), 3.98 (s, 1H), 3.81 (q, *J* = 5.49 Hz, 1H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 200.3, 162.5 (d, *J* = 244.6 Hz), 138.2, 131.3 (d J = 7.60 Hz), 125.2 (d, *J* = 2.68 Hz), 120.5 (d, *J* =

21.1 Hz), 115.5 (d, *J* = 22.5 Hz), 75.3, 64.3. **IR**: 3350 (s), 2922 (s), 2854 (m), 1681 (s), 1588 (s) cm^{-1}. **HRMS** (ESI) *m/z*: [MH^+] Calcd. for $C_9H_{10}O_3F$ 185.0608; Found 185.0607.

1-(4-Chlorophenyl)-2,3-dihydroxypropan-1-one (**10i**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-chlorobenzaldehyde **7i** (228 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10i** was afforded as a colorless oil (53 mg, 49% yield). Characterizations were consistent with previously reported literature.[70]

1-(4-Bromophenyl)-2,3-dihydroxypropan-1-one (**10j**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-bromobenzaldehyde **7j** (301 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10j** was afforded as a pale-yellow solid (60 mg, 45% yield). [m.p. = 143 ˚C] **^{1}H NMR** (501 MHz, DMSO) δ = 7.92 (d *J* = 8.6 Hz,

2H), 7.74 (d, *J* = 8.6 Hz, 2H), 5.38 (d, *J* = 6.5 Hz; 1H), 4.92 (dt, *J* = 6.5 Hz, 4.8 Hz, 1H), 4.83 (t J = 5.8; 1H), 3.66 (m, 1H). **^{13}C NMR** (126 MHz, DMSO) δ = 200.5, 134.9, 132.1, 131.1, 127.6, 75.2, 64.3 ppm **IR**: 3326.5 (s), 2984.4 (w), 2899.4 (w), 1674.5 (s) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. for $C_9H_9O_3BrNa$ 266.9627; Found 266.9628.

2,3-dihydroxy-1-(thiophen-3-yl)propan-1-one (**10m)**

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 3-thiophene carboxaldehyde **7m** (274 mg, 2.44 mmol), triethylamine (330 mg, 3.26 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10m** was afforded as a clear oil (32 mg, 23% yield) **^{1}H NMR** (501 MHz, $CDCl_3$) δ 8.21 (dd, J = 2.9,

1.3 Hz, 1H), 7.60 (dd, J = 5.1, 1.3 Hz, 1H), 7.43 (dd, J = 5.2, 2.9 Hz, 1H), 4.97 (dd, J = 5.0, 3.4 Hz, 1H), 4.06 (dd, J = 11.7, 3.4 Hz, 1H), 3.84 (dd, J = 11.7, 5.0 Hz, 1H), 2.28 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.15, 137.87, 133.72, 127.13, 126.90, 75.40, 65.62. **IR**: 3322.6 (s), 3098.6 (m), 2892.4 (w), 1664.2 (s), 1510.9 (m) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd for $C_7H_8O_3SNa$ 195.0086; Found 195.0083.

2,3-Dihydroxy-1-(4-methoxyphenyl)propan-1-one (**10t**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-methoxy benzaldehyde **7t** (222 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10t** was afforded as a pale-yellow oil (10.6 mg, 10% yield). Characterizations were consistent with previously reported literature.[70]

4-(2,3-Dihydroxypropanoyl)phenyl 4-methyl benzene sulfonate (**10u**)

The general procedure was followed using DHF (100 mg, 0.543 mmol), 4-tosyloxy benzaldehyde **7u** (450 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.05), compound **10u** was afforded as an off-white solid (60 mg, 33% yield). [m.p. = 85 ˚C] **^{1}H NMR** (700 MHz, DMSO) δ = 7.97 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.3, 2H), 7.47 (d, *J* = 8.2, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 5.36 (d, *J* = 6.4 Hz, 1H), 4.86 (dd, *J* = 11 Hz, 5.1 Hz, 1H), 4.80 (t, *J* = 5.8 Hz, 1H), 3.61 (m, 2H), 2.40 (s, 3H). **^{13}C NMR** (175 MHz, DMSO) δ = 200.1, 152.5, 146.6, 134.8, 131.7, 131.2, 130.8, 128,7, 75.1, 64.2, 21.7. **IR** 3368 (m), 2925 (m), 1688 (w), 1596 (s), 1500 (s) cm^{-1}. **HRMS** (ESI) m/z: [MNa^+] Calcd. For $C_{16}H_{16}O_6Na$ 359.0560; Found 359.0565.

2,3-Dihydroxy-1-(thiophen-2-yl)propan-1-one (**10r**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2-thiophenecarboxyaldehyde **7r** (182 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in CH_2Cl_2 (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10r** was afforded as a pale-yellow oil (45 mg, 48% yield). **^{1}H NMR** (501 MHz, $CDCl_3$) δ = 7.84 (dd *J* = 3.88 Hz, 1.08 Hz, 1H), 7.78 (dd, *J* = 4.92 Hz, 1.08 Hz, 1H), 7.21 (dd, *J* = 4.92 Hz, 3.88 Hz, 1H), 4.99 (dd, *J* = 5.10 Hz, 3.45 Hz, 1H), 4.07 (dd, *J* = 11.8 Hz, 3.40 Hz, 1H), 3.88 (dd, *J* = 11.8 Hz, 5.15 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 191.7, 139.6, 135.4, 133.4, 128.5, 75.2, 66.1. **IR**: 3340 (s), 2937 (w), 1657 (s), 1516 (w) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. for $C_7H_8O_3SNa$ 195.0086; Found 195.0086.

2,3-Dihydroxy-1-(furan-2-yl)propan-1-one (**10s**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), furaldehyde **7s** (157 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in CH_2Cl_2 (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10s** was afforded as a pale-yellow oil (33 mg, 39% yield). **^{1}H NMR** (501 MHz, $CDCl_3$) δ = 7.67 (dd, *J* = 1.65 Hz, 0.62 Hz, 1H), 7.40 (dd, *J* = 3.65 Hz, 0.45 Hz, 1H), 6.63 (dd, *J* = 3.65 Hz, 1.65 Hz, 1H), 4.93 (dd, *J* = 4.25 Hz, 3.50 Hz, 1H), 4.07 (dd, *J* = 11.81 Hz, 3.30 Hz, 1H), 3.96 (dd, *J* = 11.81 Hz, 4.45 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 187.6, 150.2, 147.4, 119.5, 112.8, 74.9, 64.9. **IR**: 3309 (s), 3130 (w), 2896 (w), 1662 (s), 1565 (m) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. for $C_7H_8O_4Na$ 179.0314; Found 179.0315.

C-veratroylglycol (**10t**)

The general procedure was followed using DHF dihydrate (150 mg, 0.8 mmol), vanillin **7t** (372 mg, 2.4 mmol), triethylamine (577 mg, 5.7 mmol) in THF (11 mL). After 18 h the reaction was diluted with 10%MeOH/CH2Cl2 and filtered over Amberlyst A-15 hydrogen

form resin to remove any TEA complexed with the product. The product was then purified via column chromatography on silica (10% MeOH/CH2Cl2, Rf = 0.45) to afford compound **10t** as a white solid (25 mg, 14% yield). [m.p. = 54 ˚C] Characterizations were consistent with previously reported literature.[71]

1-([1,1'-Biphenyl]-4-yl)-2,3-dihydroxypropan-1-one (**10x**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-phenylbenzaldehyde **7x** (297 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.25), compound **10x** was afforded as a colorless wax (31 mg, 24% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.50 (t, J = 7.4 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 5.22 (q, *J* = 4.6 Hz, 1H), 4.08 (m, 2H), 3.83 (dd, *J* = 11.8 Hz, 4.6 Hz, 1H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 198.9, 147.1, 139.5, 132.0, 129.2, 129.0, 128.6, 127.6, 127.3, 74.5, 65.5. **IR** 3344 (br), 2932 (w), 2882 (w), 1676 (s), 1603 (w) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. for $C_{15}H_{14}O_3Na$ 265.0835; Found 265.0838.

2,3-Dihydroxy-1-(4-(pyridine-2-yl)phenyl)propan-1-one (**10y**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-2-pyridyl benzaldehyde **7y** (299 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10y** was afforded as a pale-yellow oil (32 mg, 25% yield). **^{1}H NMR** (501 MHz, $CDCl_3$) δ = 8.76 (m, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.83 (m, 3H), 7.34 (m, 1H), 5.22 (t, *J* = 4.0 Hz, 1H), 4.07 (dd, *J* = 11.7 Hz, 3.2 Hz, 1H), 3.82 (dd, *J* = 11.7 Hz, 4.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.1, 155.7, 150.0, 144.8, 137.1, 133.4, 129.1, 127.4, 123.3,

121.2, 74.6, 65.4, **IR**: 3367 (m), 3054 (w), 2925 (m), 2854 (w), 1679 (s) cm^{-1}. **HRMS** (ESI) *m/z*: [MH^+] Calcd. For $C_{14}H_{14}O_3N$ 244.0968; Found 244.0967.

2,3-Dihydroxy-1-(3-methoxyphenyl)propan-1-one (**10z**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 3-methoxy benzaldehyde **7z** (222 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10z** was afforded as a pale-yellow oil (26 mg, 22% yield). **^{1}H NMR** (700 MHz, DMSO) δ 7.55 (dt, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.42 (m, 2H), 7.19 (ddd, *J* = 8.2 Hz, 2.7 Hz, 0.9 Hz, 1H), 5.23 (d, *J* = 6.7 Hz, 1H), 4.96 (dt, *J* = 6.6 Hz, 4.7 Hz, 1H), 4.77 (t, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 3.68 (dtd, *J* = 11.3 Hz, 6.2 Hz, 5.3 Hz, 4.2 Hz, 1H), 3.59 (ddd, *J* = 11.2 Hz, 6.0 Hz, 5.0 Hz, 1H). **^{13}C NMR** (176 MHz, DMSO) δ = 200.4, 159.3, 136.8, 129.8, 120.9, 119.0, 113.1, 74.5, 64.0, 55.3. **IR**: 3433 (br), 2940 (m), 1730 (s), 1685 (s), 1591 (m) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. for $C_{10}H_{12}O_4Na$ 219.0628; Found 219.0626.

2,3-Dihydroxy-1-(m-tolyl)propan-1-one (**10aa**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 3-toualdehyde **7aa** (196 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10aa** was afforded as a pale-yellow oil with its dihydroxyacetone isomer **17aa** (22 mg, 22% yield). **10aa**:**17aa** Ratio: (3:1). **^{1}H NMR** (700 MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 (t *J* = 7.8 Hz, 0.37H), 7.19 (d, *J* = 7.4 Hz, 0.37H), 7.13 (m, 0.45H), 5.23 (s, 0.30H), 5.17 (dd, *J* = 5.1 Hz, 3.3 Hz, 1H), 4.37 (dd, *J* = 19.5 Hz, 0.36H), 4.26 (d, J = 19.4 Hz, 0.33H), 4.07 (s, 0.80H), 4.03 (dd, *J* = 11.8 Hz, 3.3 Hz, 1H), 3.76 (dd, J = 11.8 Hz, 5.0 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 0.96H). **^{13}C NMR** (176 MHz,

$CDCl_3$) δ = 209.1, 199.5, 139.1, 139.0, 137.2, 135.1, 133.4, 129.9, 129.1, 129.0, 128.8, 127.5, 125.7, 124.1, 77.6, 74.5, 65.4, 65.1, 29.7, 21.3. **IR**: 3366 (s), 2923 (m), 1680 (s), 1604 (w) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. for $C_{10}H_{12}O_3Na$ 203.0679; Found 203.0679.

2,3-Dihydroy-1-(3-vinylphenyl)propan-1-one (**10ac**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 3-vinyl benzaldehyde **7ac** (215 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10ac** was afforded as a pale-yellow oil (22 mg, 22% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ = 7.96 (s, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 6.78 (dd, *J* = 17.6 Hz, 10.9 Hz, 1H), 5.86 (d, *J* = 17.6 Hz, 1H), 5.39 (d, *J* = 10.9 Hz, 1H), 5.19 (dd, *J* = 4.9 Hz, 3.3 Hz, 1H), 4.04 (dd, *J* = 11.8 Hz, 3.3 Hz, 1H), 3.78 (dd, *J* = 11.8 Hz, 4.9 Hz, 1H) **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.4, 138.6, 135.5, 133.8, 131.7, 129.2, 127.7, 126.3, 116.0, 74.6, 65.3. **IR**: 3338 (s), 2923 (m), 2854 (m), 1680 (s) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. for $C_{11}H_{12}O_3Na$ 215.0678; Found 215.0679.

2-(2,3-Dihydroxy propanoyl)phenyl 4-methyl benzene sulfonate (**10ad**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2-tosyloxy benzaldehyde **7ad** (450 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10ad** was afforded as an off-white solid with its dihydroxyacetone isomer **17ad** (40 mg, 22% yield). **10ad**:**17ad** Ratio (1:1). [m.p. = 98 ˚C] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.65 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.54 (ddd, *J* = 8.2 Hz, 7.4 Hz, 1.8 Hz, 1H), 7.41 (m, 3H), 7.35 (dd, *J* = 7.8 Hz, 3.1 Hz, 2H), 7.32 (td, *J* = 3.2 Hz, 1.7 Hz,

2H), 7.20 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H), 7.06 (ddd, *J* = 5.0 Hz, 3.3 Hz, 1.6 Hz, 1H), 5.50 (d, *J* = 2.1 Hz, 1H), 5.05 (d, *J* = 3.1 Hz, 1H), 4.46 (d, *J* = 19.8 Hz, 1H), 4.30 (d, *J* = 19.8 Hz, 1H), 3.88 (dd, *J* = 12.2 Hz, 3.5 Hz, 1H), 3.80 (d, *J* = 4.7 Hz, 1H), 3.69 (dd, *J* = 12.2 Hz, 3.4 Hz, 1H), 2.50 (s, 3H), 2.49 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.7, 200.3, 147.3, 146.5, 146.2, 133.8, 132.2, 131.3, 131.3, 130.6, 130.4, 130.2, 130.1, 130.0, 129.3, 128.7, 128.6, 128.5, 128.0, 127.8, 123.5, 122.7, 76.9, 72.0, 65.7, 63.6, 21.8, 21.8. **IR**: 3386 (w), 2926 (w), 1596 (m) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. For $C_{16}H_{16}O_6Na$ 359.0560; Found 359.0564.

2,3-Dihydroxy-1-(o-tolyl)propan-1-one (**10ae**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2-tolualdehyde **7ae** (196 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.25), compound **10ae** was afforded as a pale-yellow oil with its dihydroxyacetone isomer **9v** (22 mg, 22% yield). **10ae**:**17ae** Ratio: (2:1). **^{1}H NMR** (700 MHz, $CDCl_3$) δ = 7.55 (dd, *J* = 7.6 Hz, 1.0 Hz, 1H), 7.46 (td, *J* = 7.6 Hz, 1.0 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.28 (m, 1.20H), 7.24 (m, 0.85H), 5.43 (s, 0.73H), 5.06 (d, *J* = 2.9 Hz, 1H), 4.34 (d, *J* = 19.3 Hz, 0.36H), 4.20 (d, *J* = 19.3 Hz, 0.36H), 4.13 (d, *J* = 3.3 Hz, 0.61H), 3.93 (dd, *J* = 11.8 Hz, 3.2 Hz, 1H), 3.69 (dd, *J* = 11.8 Hz, 3.5 Hz, 1H), 2.51 (s, 3H), 2.40 (s,

1H) **^{13}C NMR** (175 MHz, $CDCl_3$) δ = 209.6, 203.1, 139.2, 136.4, 135.3, 134.0, 132.32, 132.30, 131.5, 129.2, 128.1, 128.0, 126.8, 125.8, 75.8, 65.3, 64.6, 20.7, 19.3. **IR**: 3404 (br), 2928 (m), 1690 (s) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. For $C_{10}H_{12}O_3Na$ 203.0679; Found 203.0677.

1-(3,4-Dimethylphenyl)-2,3-dihydroxypropan-1-one (**10af**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 3,4-dimethylbenzaldehyde **7af** (219 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10af** was afforded as a pale-yellow oil (18 mg, 17% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.26 (s, 1H), 5.13 (m, 1H), 4.02 (d, *J* = 5.8 Hz, 1H), 4.00 (s, 1H), 3.71 (dd, *J* = 11.8 Hz, 5.2 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 198.9, 144.3, 137.6, 131.2, 130.1, 129.6, 126.3, 74.3, 65.6, 20.2, 19.8. **IR**: 3422 (br), 2924 (s), 2856 (w), 2154 (w), 2015 (w), 1975 (w), 1678 (s), 1607 (m), 1566 (w) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. For $C_{11}H_{14}O_3Na$ 217.0835; Found 217.0836.

1-(2,6-Difluorophenyl)-2,3-dihydroxypropan-1-one (**10ah**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2,6-difluorobenzaldehyde **7ah** (231 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10ah** was afforded as a pale-yellow oil (34 mg, 31% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.49 (tt, *J* = 8.5 Hz, 6.3 Hz, 1H), 6.99 (t, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 16.9 Hz, 1H), 5.29 (dd, *J* = 7.9 Hz, 4.4 Hz, 1H), 4.58 (dq, *J* = 4.8 Hz, 1.5 Hz, 1H), 4.33 (t, *J* = 7.9 Hz, 1H), 3.93 (d, *J* = 4.8 Hz, 1H), 2.76 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 196.01, 161.38 (dd, *J* = 250.3, 8.0 Hz), 160.57 (dd, *J* = 257.0, 6.4 Hz), 134.37 (d, *J* = 11.0 Hz), 130.55 (d, *J* = 10.4 Hz), 112.50 (dd, *J* = 22.2, 3.8 Hz), 112.03 (dd, *J* = 22.0, 4.0 Hz), 73.52, 67.83. **IR**: 3439 (br), 2986 (w), 1724 (s), 1625 (m), 1592 (w) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. For $C_9H_8O_3F_2Na$ 225.0334; Found 225.0336.

2,3-Dihydroxy-1-(naphthalen-2-yl)propan-1-one (**10ai**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2-naphthaldehyde **7ai** (255 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10ai** was afforded as a pale-yellow oil (46 mg, 39% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.49 (m, 1H), 7.99 (m, 4H), 7.93 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H), 7.68 (ddd, *J* = 8.2 Hz, 6.9 Hz, 1.3 Hz, 1H), 7.62 (ddd, *J* = 8.1 Hz, 6.9 Hz, 1.3 Hz, 1H), 5.35 (td, *J* = 5.3 Hz, 3.3 Hz, 1H), 4.13 (d, *J* = 3.3 Hz, 1H), 4.10 (t, *J* = 5.2 Hz, 1H), 3.84 (dd, *J* = 11.8 Hz, 5.2 Hz, 1H), 2.27 (s, 1H), 1.60 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 199.3, 136.1, 132.4, 130.7, 130.6, 129.7, 129.2, 129.1, 127.9, 127.3, 123.8, 74.6, 65.6. **IR**: 3337 (m), 2926 (w), 1678 (s), 1626 (w) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. For $C_{13}H_{12}O_3Na$ 239.0679; Found 239.0676.

2,3-Dihydroxy-1-(1-methyl-1H-indol-2-yl)propan-1-one (**10ak**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2-indolecarboxyaldehyde **7ak** (259 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in CH_2Cl_2 (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10ak** was afforded as a yellow wax (18 mg, 15% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 1H), 7.40 (m, 2H), 7.31 (s, 1H), 7.18 (ddd, *J* = 7.9 Hz, 6.6 Hz, 1.2 Hz, 1H), 5.29 (s, 1H), 5.08 (s, 1H), 4.09 (m, 1H), 4.07 (s, 3H), 3.86 (dd, *J* = 11.6 Hz, 5.1 Hz, 1H), 2.90 (d, *J* = 19.6 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 191.8, 140.5, 131.2, 126.9, 125.9, 123.2, 121.3, 112.7, 110.5, 74.8, 66.9, 32.2. **IR**: 3420 (br), 2926 (m), 1656 (s), 1513 (w) cm^{-1}. **HRMS** (ESI) *m/z*: [MNa^+] Calcd. For $C_{12}H_{13}O_3NNa$ 242.0788; Found 242.0787.

methyl 4-(hydroxymethyl)benzoate (**18k**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-methylcarboxy benzaldehyde (268 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in

CH_2Cl_2 (7 mL). Only the benzyl alcohol observed by crude NMR after 18hrs of reaction time.

(4-nitrophenyl)methanol (**18l**)

The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-nitro benzaldehyde (246 mg, 1.63 mmol), and triethylamine (220, 2.17) in CH_2Cl_2 (7 mL). Only the benzyl alcohol observed by crude NMR after 18hrs of reaction time

General Procedure for the Synthesis of (Hetero)aryl 2,3 dihydroxypropionic methyl esters:

A dried round bottom flask is charged with nitrogen and 4 eq of NaOH. To this, 5 mL of distilled water is added and stirred to fully dissolve the salt. Aldehyde is dissolved to X M in distilled THF in a vial. In a second separate vial, 1 eq of DHF and 2 eq of LiOH are dissolved in water to bring the concentration of LiOH to 1M (2mL). The aldehyde solution is added to the reaction flask followed by slow addition of DHF/LiOH solution via syringe pump. Volume is added over 30 min. The reaction is then allowed to stir overnight. After ~18hrs, Amberlyst A-15 cationic exchange resin is added to the flask. Stirring is continued until the pH of the solution reaches ~4. Usual equilibration of pH takes approximately 20 min depending on amount of resin beads added. The mixture was poured over a Buchner funnel to remove the beads and washed with both water and Ethyl Acetate. The biphasic mixture was separated via a separatory funnel and the aqueous phase was extracted 3 times with ethyl acetate to remove all undesired Cannizzaro reaction products. The aqueous phase contains both the dihydroxy acid products as well as DHF dimerization/fragmentation products (tartrate, glycolate, hydroxy malonate). After concentration of the aqueous phase through rotatory evaporation, the crude mixture was

suspended in MeOH and transferred into another round bottom flask. Catalytic concentrated sulfuric acid (5 drops) was added and the reaction mixture refluxed for 5 hrs. After completion by TLC, the reaction was concentrated onto silica and purified via flash chromatography (5 % MeOH/DCM).

methyl 2,3-dihydroxy-3-phenylpropanoate (**14a**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), benzaldehyde **8a** (259 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.2), compound **14a** was afforded as a clear oil (93 mg, 58% yield) in a 1:1 mixture of diastereomers. Characterization matches previously published results.[72]

methyl 2,3-dihydroxy-3-(p-tolyl)propanoate (**14c**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-methyl benzaldehyde **8c** (294 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.25), compound **14c** was afforded as a clear oil (108 mg, 63% yield) in a 1:1 mixture of diastereomers. Characterization matches previously published results[72].

methyl 3-(4-ethylphenyl)-2,3-dihydroxypropanoate (**14d**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-ethyl benzaldehyde **8d** (328 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.25), compound **14d** was afforded as a clear oil (69 mg, 38% yield) as a 1:1 mixture of diastereomers. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.89 (d, J = 8.2 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.36 – 7.33 (m, 2H), 7.19 (d, J = 8.0 Hz, 2H), 5.15 (dd, J = 7.2, 3.3

Hz, 1H), 4.55 (d, J = 3.3 Hz, 1H), 3.79 (d, J = 7.2 Hz, 1H), 2.76 (q, J = 7.6 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H), 1.24 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 150.88, 150.71, 144.21, 128.97, 128.88, 128.68, 128.23, 128.18, 127.85, 127.82, 127.61, 127.52, 127.44, 85.52, 84.27, 76.15, 57.28, 29.71, 29.03, 28.58, 28.55, 15.48, 15.44, 15.09, 15.06. **IR** 3418.8 (br), 1975.0 (s), 2128.3 (w), 1738.4 (w), 1684.9 (s), 1613.5 (w) **HRMS** (ESI) *m/z* for $C_{12}H_{16}O_4Na$: Calcd 247.0941; found 247.0941.

methyl 2,3-dihydroxy-3-(4-isopropylphenyl)propanoate (**14e**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-isopropyl benzaldehyde **8e** (362 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH{\cdot}H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.25), compound **14e** was afforded as a trace <5% yield.

methyl 3-(4-fluorophenyl)-2,3-dihydroxypropanoate (**14f**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-fluoro benzaldehyde **8f** (303 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH{\cdot}H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14f** was afforded as a pale-yellow oil (112 mg, 64% yield) as a 1:1 mixture of diastereomers. Characterization matches previously published results[73].

methyl 3-(3-fluorophenyl)-2,3-dihydroxypropanoate (**14g**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 3-fluoro benzaldehyde **8g** (303 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH{\cdot}H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14g** was afforded as a pale-yellow oil (69 mg, 40% yield) as a 1:2 mixture of diastereomers. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.35 (m, 1H), 7.32

(m, 0.51H), 7.17 (m, 1.95H), 7.08 (m, 1H), 7.02 (m, 1.32H), 5.04 (d, J = 2.9 Hz, 1H), 5.03 (d, J = 4.7 Hz, 0.44H), 4.50 (d, J = 4.2 Hz, 0.46H), 4.38 (d, J = 2.8 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 1.33H), 3.28 (s, 1H), 3.18 (s, 0.73H), 2.99 (s, 1H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 172.95, 172.20, 162.89 (d, J = 246.3 Hz), 162.76 (d, J = 246.3 Hz), 142.64 (d, J = 7.1 Hz), 141.28 (d, J = 7.2 Hz), 129.99 (d, J = 8.3 Hz), 129.81 (d, J = 8.1 Hz), 121.95 (d, J = 3.1 Hz), 121.75 (d, J = 2.8 Hz), 115.12, 114.94 (d, J = 20.9 Hz), 113.48 (d, J = 22.3 Hz), 113.40 (d, J = 22.2 Hz), 74.68, 74.51, 74.40 (d, J = 1.7 Hz), 73.77 (d, J = 1.7 Hz), 53.01, 52.56. **IR** 3425.1 (br), 2954.6 (m), 1734.3 (s), 1613.1 (m), 1590.5 (s). **HRMS** (ESI) Calcd for $C_{10}H_{11}O_4FNa$ 237.0534; observed 237.0536

methyl 3-(2-fluorophenyl)-2,3-dihydroxypropanoate (**14h**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 2-fluoro benzaldehyde **8h** (303 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH{\cdot}H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14h** was afforded as a pale-yellow oil (77 mg, 44% yield) as a 1:2 mixture of diastereomers: **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.54 (td, J = 7.6, 1.7 Hz, 1H), 7.48 (td, J = 7.6, 1.7 Hz, 0.41H), 7.31 (tdd, J = 8.6, 4.1, 1.5 Hz, 1.26H), 7.20 (td, J = 7.5, 1.1 Hz, 1H), 7.17 (td, J = 7.5, 1.1 Hz, 0.45H), 7.08 – 7.02 (m, 1.32H), 5.36 (d, J = 2.9 Hz, 1H), 5.33 (d, J = 3.9 Hz, 0.42H), 4.56 (d, J = 3.9 Hz, 0.45H), 4.42 (d, J = 2.9 Hz, 1H), 3.86 (s, 3H), 3.66 (s, 1.32H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 173.02, 172.45, 159.69 (d, J = 245.4 Hz), 159.55 (d, J = 245.2 Hz), 129.55 (d, J = 8.3 Hz), 129.51 (d, J = 8.4 Hz), 128.00 (d, J = 4.0 Hz), 127.92 (d, J = 3.9 Hz), 127.14 (d, J = 13.0 Hz), 124.24 (d, J = 3.5 Hz), 124.07 (d, J = 3.5 Hz), 115.12 (d, J = 21.5 Hz), 115.08 (d, J = 22.0 Hz), 73.92, 73.65, 69.64 (d, J = 1.4 Hz), 68.82 (d, J = 2.3 Hz), 53.02, 52.44. **IR**: 3434.3 (br), 2953.0

(m), 1744.6 (s), 1619.6 2:(m), 1587.2 (m). **HRMS** (ESI) Calcd for $C_{10}H_{11}O_4FNa$ 237.0534; observed 237.0533.

methyl 3-(4-chlorophenyl)-2,3-dihydroxypropanoate (**14i**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-chloro benzaldehyde **8i** (344 mg, 2.44 mmol) in 2mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14i** was afforded as a pale-yellow oil (115 mg, 61% yield) as a 3:2 mixture of diastereomers. Characterizations matches previously published results[73].

methyl 3-(4-bromophenyl)-2,3-dihydroxypropanoate (**14j**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-bromo benzaldehyde **8j** (452 mg, 2.44 mmol) in 2mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14j** was afforded as a pale-yellow oil (152 mg, 68% yield) as a 3:2 mixture of diastereomers. Characterization matches previously published results[74].

methyl 4-(1,2-dihydroxy-3-methoxy-3-oxopropyl)benzoate (**14k**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-methylcarboxy benzaldehyde **8k** (401 mg, 2.44 mmol) in 2mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14k** was afforded as a pale-yellow wax (51 mg, 25% yield) as a 2:1 mixture of diastereomers. **^{1}H NMR** (700 MHz, DMSO-d6) δ 7.86 (d, J = 7.7 Hz, 3H), 7.36 (dd, J = 8.1, 3.6 Hz, 3H), 4.87 (d, J = 3.9 Hz, 1H), 4.67 (d, J = 7.2 Hz, .87H), 4.18 (d, J = 3.9 Hz, 1H), 4.02 (d, J = 7.2 Hz, .93H), 3.62 (s, 2H), 3.59 (s, 3H), 3.38 (s, 6H). **^{13}C NMR** (176 MHz, DMSO) δ 173.40, 173.07, 129.08, 129.04, 127.02, 126.52,

75.92, 75.86, 74.43, 74.33, 53.29, 51.88, 51.70. **IR** 3364.8 (br), 2956.3 (m), 1698.8 (m), 1612.2 (m). **HRMS** (ESI) Calcd for $C_{12}H_{14}O_6Na$ 277.0683; found 277.0684.

methyl 2,3-dihydroxy-3-(4-nitrophenyl)propanoate (**14l**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-nitro benzaldehyde **8l** (369 mg, 2.44 mmol) in 2mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, $R_f = 0.15$), compound **14l** was afforded as a yellow wax (81 mg, 41% yield) as a 4:3 mixture of diastereomers. Characterization matches previously published results[74].

methyl 2,3-dihydroxy-3-(thiophen-3-yl)propanoate (**14m**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 3-thiophene carboxaldehyde **8m** (274 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, $R_f = 0.15$), compound **14m** was afforded as a pale-yellow oil (53 mg, 32% yield) as a 3:2 mixture of diastereomers. Characterization matches previous published results.[75]

methyl 2,3-dihydroxy-3-(pyridin-2-yl)propanoate (**14n**)

The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 2-pyridyl carboxaldehyde **8n** (261 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and $LiOH \cdot H_2O$ (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, $R_f = 0.15$), compound **14n** was afforded as a pale-yellow oil (69 mg, 43% yield) as a 2:1 mixture of diastereomers. **^{1}H NMR** (700 MHz, $CDCl_3$ & MeOD) δ 8.55 (dt, J = 4.9, 1.4 Hz, 1H), 8.52 (dt, J = 4.9, 1.3 Hz, 0.49H), 7.76 (td, J = 7.7, 1.7 Hz, 1H), 7.71 (ddd, J = 19.0, 7.7, 1.7 Hz, 0.54H), 7.44 (dd, J = 7.9, 1.1 Hz, 1H), 7.38 (d, J = 7.8 Hz,

1.45H), 7.26 (m, 1.4H), 5.13 (d, J = 2.2 Hz, 1H), 5.05 (d, J = 4.2 Hz, 0.5H), 4.60 (d, J = 2.2 Hz, 1H), 4.57 (d, J = 4.2 Hz, 0.59H), 3.85 (s, 3H), 3.67 (s, 1.7H). **^{13}C NMR** (176 MHz, $CDCl_3$ & MeOD) δ 173.03, 172.33, 158.03, 157.84, 148.42, 148.11, 137.09, 136.95, 122.99, 122.90, 121.50, 120.84, 75.04, 74.10, 73.91, 73.30, 52.73, 52.23.**IR** 3307.2 (br), 2925.0 (m), 2855.7 (w), 1640.7 (m)

Picrasidine Y (**9n**)

The general procedure was followed using DHF dihydrate (100 mg, 0.814 mmol), 9*H*-pyrido [3,4-*b*] indole-1-carbaldehyde **8o** (479 mg, 2.44 mmol) in 2mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH·H2O (68 mg, 1.63 mmol) in deionized water. Isolated as a crude mixture from the aqueous phase. Esterification attempted but unable to isolate pure product.

Procedure for Iterative Multi-day Reactions

The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), aldehyde 7 (1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After 18 h, the reaction was cooled to room temperature, DHF dihydrate (100 mg, 0.543 mmol) was added, and the reaction was returned to reflux for another 18 h. At that time, the reaction was again cooled to room temperature, another equivalent of DHF dihydrate (100 mg, 0.542 mmol) was added, and the reaction was returned to reflux for another 18 h. This gave a final reaction stoichiometry of 1:1 (aldehyde/DHF). After the final iteration, the reaction was diluted with CH_2Cl_2, concentrated under reduced pressure, and purified by column chromatography on silica gel using EtOAc/Hexanes as the mobile phase. Note: Cooling of the reaction before each addition of DHF is essential as adding DHF directly to

the hot reaction mixture leads to rapid breakdown of the DHF and no improvements in yield.

C-veratroylglycol Experimental Procedures

4-formyl-2-methoxyphenyl 4-methylbenzenesulfonate **29**

In a nitrogen flushed flask, vanillin (1g, 6.6mmol), was dissolved in 20mL of freshly distilled DCM (0.3M). 4 eq of triethylamine (0.99g, 26mmol) was added and the mixture was cooled to 0°C in an ice bath. Tosyl chloride (1.99g, 7.2mmol) was slowly added to the mixture and the reaction was allowed to warm overnight. After completion, the reaction was acidified with 1M HCl to a pH of ~4. The organic layer was washed twice with 1M HCl and once with saturated $NaHCO_3$. Combined organic layers were dried with Mg_2SO_4 and filtered through celite. Concentration of the solution provided the title compound in quantitative yield (2.4g). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.77 (d, J = 8.3 Hz, 2H), 7.44 (dd, J = 8.1, 1.8 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.33 (d, J = 7.7 Hz, 1H), 3.65 (s, 3H), 2.47 (s, 3H). **^{13}C NMR** (176 MHz, CDCl3) δ 190.81, 152.56, 145.44, 142.97, 135.71, 132.86, 129.47, 128.55, 124.51, 124.31, 110.96, 55.75, 21.69.

4-(2,3-dihydroxypropanoyl)-2-methoxyphenyl 4-methylbenzenesulfonate **10aj**

Synthesized following standard DHF decarboxylation method. Using 0.1g of DHF hydrate (0.5mmol) dissolved in 5mL of THF, 3eq of 4-Ts vanillin (0.5g, 1.5mmol) and 4eq of TEA (0.22g, 2.2mmol) were added to the mixture. The reaction was refluxed overnight. After 18hrs, the reaction was concentrated onto silica and column using 50% EtOAc in Hexanes. 51mg were isolated at a 32% yield. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.81 – 7.70 (m, 2H), 7.52 – 7.41 (m, 1H), 7.36 – 7.28 (m, 4H), 5.13 (dd, J = 4.5, 2.5 Hz, 1H), 4.05 – 3.94 (m, 2H), 3.79 (dd, J = 11.9, 4.5 Hz, 1H), 3.65 (d, J = 1.1 Hz, 3H), 2.47 (s, 3H). **^{13}C NMR** (176

MHz, CDCl3) δ 198.34, 152.48, 145.57, 142.80, 132.91, 132.86, 129.57, 128.58, 128.56, 124.27, 121.44, 112.34, 74.52, 65.27, 60.44, 55.85, 21.73.

4-(3-((tert-butyldimethylsilyl)oxy)-2-hydroxypropanoyl)-2-methoxyphenyl 4-methyl benzene sulfonate **32**

In a nitrogen charged flame dried flask, O-Ts *C*-veratroylglycol (2.6g, 7.7mmol) was dissolved in DCM (20mL). Sequentially, TBSCl (1.16g, 7.7mmol) and imidazole (0.79g, 11.6mmol) were added and the reaction was stirred overnight. The solution was acidified with NH_4Cl and diluted with EtOAc followed by extraction of the aqueous phase with EtOAc. The combined organic layers were dried with Na_2SO_4 and purified via flash chromatography with 50% EtOAc in hexanes. 3.2g (85% yield) was isolated.

(E)-4-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2,6-dimethoxyphenol **33**

Syrulic acid was dissolved in THF and 1 eq of LAH was added. After 6 hrs the reaction was acidified with 1M HCl at 0°C and diluted with EtOAc. Organic layers were dried with Na_2SO_4 filtered, and concentrated. Crude mixture used without further purification. In a nitrogen charged flame dried flask, allyl alcohol (1.5g, 7.1mmol) was dissolved in DMF (20mL). Sequentially, TBSCl (1.1g, 7.1mmol) and imidazole (0.73g, 10.7mmol) were added and the reaction was stirred overnight. The solution was acidified with NH_4Cl and diluted with EtOAc followed by extraction of the aqueous phase with EtOAc. The combined organic layers were washed twice with brine and dried with Na_2SO_4 followed by filtration through celite. The product was purified via flash chromatography 20% EtOAc in hexanes isolating 1.3g (55% yield) over the two steps. Characterization corresponds to previous published results.[76]

4-(3-((tert-butyldimethylsilyl)oxy)propyl)-2-methoxyphenol **34**

In a nitrogen charged flame dried flask, alcohol (2g, 10.9mmol) was dissolved in DCM (20mL) and cooled to 0°C. Sequentially TBSCl (1.7g, 10.9mmol) and imidazole (1.1g, 16.4mmol) were added and the reaction was stirred overnight. The reaction was acidified with NH_4Cl and the aqueous phase was extracted with DCM. The combined organic layers were washed with NH_4Cl and dried over Na_2SO_4. The product was purified by flash chromatography 20%EtOAc in hexanes to provide 1.7g (53% yield) of product. Characterization corresponds to previous published results.[77]

Glyoxylate Dimer Experimental Procedures

N-Benzyl thymidine **35**

In a nitrogen charged flame dried flask, thymidine (5g, 20.6mmol) was dissolved in DMSO (50mL). To this solution, benzyl bromide (5.3g, 30.9mmol) and potassium carbonate (4.3g, 30.9mmol) were added and the mixture was stirred at room temperature for 24hrs. At which time, the reaction was acidified with NH_4Cl and diluted into EtOAc. The aqueous phase was extracted twice with EtOAc then the combined organic layers were washed twice with brine. The organic phase was dried with Na_2SO_4 and filtered through celite. Product was isolated via flash chromatography with 5%MeOH in DCM with 3.4g recovered (50% yield). Corresponds to previous published characterization.[78]

5'-(tert-butyldimethylsilyl)-N-benzyl thymidine **36**

In a nitrogen charged flame dried flask, N^1-benzyl thymidine (1.6g, 4.8mmol) was dissolved in DMF (25mL). Sequentially, TBSCl (1.0g, 6.7mmol) and imidazole (0.49g, 7.2mmol) were added and the solution was stirred at room temperature overnight. The reaction was acidified with NH_4Cl and diluted with EtOAc. The aqueous phase was extracted twice with EtOAc followed by twice washing of the combined organic layers

with brine. The organic phase was dried over Na_2SO_4 and filtered through celite. Product was isolated via flash chromatography with 3%MeOH in DCM with 1.4g recovered (65% yield). Corresponds to previous published characterization.[79]

5'-(tert-butyldiphenylsilyl) thymidine **37**

Synthesized directly from published method. Characterization confirmed synthesis.[80]

5'-dimethoxytrityl-N-benzyl thymidine **39**

In a nitrogen charged flame dried flask, N^1-benzyl thymidine (0.5g, 1.5mmol) was dissolved in DCM (15mL). Sequentially, TEA (0.38g, 3.8mmol) and DMTrCl (0.56g, 1.7mmol) was added and the reaction was stirred at room temperature overnight. The reaction was quenched with $NaHCO_3$ and the aqueous phase was extracted with DCM. The combined organic layers were washed with NH_4Cl, dried over Na_2SO_4 and filtered through celite. Product was isolated via flash chromatography with 2%MeOH in DCM with 0.84g recovered (88% yield). Characterization corresponded to previously published results[81].

5'-dimethoxytrityl-3'-(tert-butyldimethylsilyl)-N-benzyl thymidine **40**

In a nitrogen charged flame dried flask, N^1-benzyl 5'-DMTr thymidine (1.6g, 2.5mmol) was dissolved in DMF (25mL). Sequentially, TBSCl (0.38g, 2.5mmol) and imidazole (0.49g, 7.2mmol) were added and the solution was stirred at room temperature overnight. The reaction was acidified with NH_4Cl and diluted with EtOAc. The aqueous phase was extracted twice with EtOAc followed by twice washing of the combined organic layers with brine. The organic phase was dried over Na_2SO_4 and filtered through celite. Product was isolated via flash chromatography with 3%MeOH in DCM with 1.2g recovered (65% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 – 7.35 (m, 5H), 7.35 – 7.18 (m, 7H), 7.13 –

6.98 (m, 2H), 6.89 – 6.72 (m, 3H), 6.49 – 6.29 (m, 1H), 5.28 (s, 0H), 5.11 (s, 2H), 4.58 – 4.39 (m, 2H), 4.01 (d, J = 3.4 Hz, 1H), 3.78 (d, J = 9.3 Hz, 3H), 3.50 – 3.30 (m, 1H), 2.59 – 2.23 (m, 1H), 1.94 (s, 1H), 1.47 (s, 1H), 0.91 (s, 2H), 0.10 (s, 2H).

3'-(tert-butyldimethylsilyl)-N-benzyl thymidine **41**

In a flask, protected thymidine (1.2g, was dissolved in DCM and catalytic TFA was added and the reaction was stirred for 1 hr. Color change indicated deprotection of DMTr group. The mixture was basified with $NHCO_3$ and dried with Na_2SO_4. The product was purified via flash chromatography with 0.44g (62% yield) isolated with 2% MeOH in DCM. Used without further purification.

5'-(tert-butyldimethylsilyl)-3',N-dibenzyl thymidine **42**

In a nitrogen charged flame dried flask, 5' TBS thymidine (2g, 4.1mmol) was dissolved in DMSO (30mL). To this solution, benzyl bromide (1.8g, 10.4mmol) and potassium carbonate (2.3g, 16.6mmol) were added and the mixture was stirred at room temperature for 24hrs. At which time, the reaction was acidified with NH_4Cl and diluted into EtOAc. The aqueous phase was extracted twice with EtOAc then the combined organic layers were washed twice with brine. The organic phase was dried with Na_2SO_4 and filtered through celite. Product was isolated via flash chromatography with 2%MeOH in DCM with 1.8g recovered (65% yield). Product was used in the next step without further purification.

3', N-dibenzyl thymidine **43**

The previous compound (0.350g, 0.5mmol) was dissolved in 6 mL of THF at room temperature in a nitrogen charged flame dried flask. To this solution was added *tetra*-butylammonium fluoride (0.275g, 1.1mmol) as a 1M solution in THF. This mixture was monitored by TLC until full deprotection of the TBDPS alcohol was observed by TLC.

The mixture was diluted with DCM and washed twice with brine. The aqueous phase was extracted in to another portion of DCM and the combined organic layers were dried over Na_2SO_4 and concentrated onto silica. The title compound was purified via flash chromatography using 2% MeOH in DCM at 75% yield (0.158g). Characterization corresponded to previously published literature.[82]

Acid Catalyzed Acetalizations

In a nitrogen charged flame dried flask, protected thymidine (2 eq) and respective glyoxylate derivative (1 eq) were dissolved in MePh (0.2M). 20 mol% of the acid catalyst was added and the reaction was refluxed under a Dean-Stark apparatus overnight. No reaction was observed by TLC and starting material was fully recovered.

Dichloroacetate

methyl 2-((2-(((tert-butyldimethylsilyl) oxy)methyl) -5-(5-methy l-2,4-dioxo-3,4-dihydropyrimidin- 1(2H)-yl) tetrahydrofuran-3-yl)oxy) -2-chloroacetate **44**

In a nitrogen charged flame dried flask, dichloromethylacetate (0.06g, 0.4mmol) and 5"-TBS thymidine (0.49g, 1.4mmol) were dissolved in MeCN (15mL). Silver carbonate was added and the reaction was refluxed overnight. After completion the reaction was filtered through celite and purified via column chromatography using 50% EtOAc in hexanes. Purification provided 0.037g (26% yield) was isolated. **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.53 – 7.38 (m, 4H), 7.32 – 7.14 (m, 10H), 5.42 (s, 1H), 5.10 (s, 2H), 4.57 (dd, J = 6.3, 4.4 Hz, 1H), 4.03 – 3.92 (m, 2H), 3.88 (dd, J = 5.5, 3.1 Hz, 3H), 3.53 (q, J = 7.3 Hz, 3H), 2.66 (q, J = 7.2 Hz, 4H), 2.46 – 2.26 (m, 3H), 1.93 (d, J = 1.2 Hz, 5H), 1.43 (t, J = 7.3 Hz, 4H), 1.12 (t, J = 7.2 Hz, 5H).

5-(3-benzyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-yl 2,2-dichloroacetate **45**

In a nitrogen charged flame dried flask, 5'-TBS-N^1-benzyl thymidine (0.150g, 0.3mmol) was dissolved in MeCN (15mL) with dichloro methylacetate (0.08g, 0.5mmol). To this solution, potassium carbonate (0.093g, 0.7mmol) and the solution was refluxed overnight. The reaction mixture was filtered through celite and purified via flash chromatography with 0.153g (41% yield) isolated. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 1H), 7.26 (d, J = 0.4 Hz, 10H), 6.42 (dd, J = 9.3, 5.2 Hz, 1H), 5.95 (s, 0H), 5.37 (d, J = 6.3 Hz, 1H), 5.12 (s, 2H), 4.14 (s, 1H), 3.92 (d, J = 2.0 Hz, 1H), 2.51 (dd, J = 14.1, 5.3 Hz, 1H), 2.16 (ddd, J = 14.1, 9.3, 6.1 Hz, 1H), 1.94 (d, J = 1.4 Hz, 2H), 1.25 (s, 6H), 0.95 – 0.90 (m, 7H), 0.13 (d, J = 0.3 Hz, 2H), 0.06 (d, J = 0.3 Hz, 7H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.70, 168.78, 156.46, 142.31, 138.38, 134.73, 133.90, 133.15, 116.24, 90.74, 90.18, 84.18, 69.35, 69.00, 50.09, 35.23, 31.42, 23.82, 18.84, 6.55, 0.14, -0.00.

BHT-ester reaction

In a nitrogen charged flame dried flask, 1 eq of protected thymidine was dissolved into MeCN (15mL) with dichloro BHT-acetate (2 eq) and silver carbonate (4 eq). The reaction was refluxed overnight. A silver mirror formed on the flask and after concentration of the reaction mixture it was determined that oxidation and removal of the BHT group. The instability led away from this group.

Model test

2,2-bis(benzyloxy)acetonitrile **45b**

In a nitrogen charged flame dried flask, dichloroacetonitrile (0.3g, 2.7mmol) and benzyl alcohol (0.89g, 8.1mmol) were dissolved in MeCN (15mL). Silver carbonate (3.8g,

13.6mmol) was added and the reaction was refluxed overnight. The reaction was filtered through celite and purified via column chromatography to provide 0.38g (55% yield) of product.

Base-Promoted dichloroacetonitrile tests

In a nitrogen charged flame dried flask, dichloroacetonitrle (1 eq, 0.1g), various protected thymidine (3 eq) and base (5 eq) were all combined in MeCN (15mL). The reaction was refluxed overnight. After completion, filtration of the solution was followed by TLC and crude NMR analysis.

2-((2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl)oxy)-2-chloroacetonitrile **46**

In a nitrogen charged flame dried flask, 5'-TBS thymidine (0.35g, 1.0mmol) and dichloroacetonitrile (.238g, 2.5mmol) were dissolved in 10mL of MeCN. Silver carbonate (0.81g, 5mmol) was added and the reaction was refluxed overnight. After completion, the solution was filtered through celite and purified via column chromatography to provide 0.14g (32% yield) of product. **^{1}H NMR** (300 MHz,$CDCl_3$) δ 8.30 (s, 1H), 7.58 (s, 0H), 6.38 (dd, J = 9.3, 5.2 Hz, 1H), 5.93 (dd, J = 6.1, 0.7 Hz, 1H), 5.37 (d, J = 6.0 Hz, 1H), 4.20 (s, 0H), 4.00 – 3.86 (m, 1H), 2.51 (dd, J = 13.9, 5.3 Hz, 1H), 1.92 (s, 2H), 0.93 (d, J = 1.1 Hz, 8H), 0.13 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.45, 135.14, 111.20, 85.01, 84.70, 78.56, 65.27, 37.98, 25.93, 18.35, 12.51, -5.37, -5.46.

Fluoride Tests

In a nitrogen charged flame dried flask, 5'TBS-3,N-dibenzyl thymidine (2.1 eq) was dissolved in THF (0.5M) at room temperature. The respective fluoride source (2.1 eq) was

added followed by dichloroacetonitrile (1 eq). The reaction was followed by TLC. Full desilylation was observed but no substitution seen by TLC or crude NMR.

Glyoxylate Acetal Stability

Ethyl-2-((2-(((tert-butyldimethylsilyl)oxy)methyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl)oxy)-2-ethoxyacetate

In a nitrogen charged flame dried flask, 5'-TBS thymidine was dissolved in MeCN

In an open round bottom flask, the mixed acetal was dissolved in a solution of MeOH and H_2SO_4 with a pH of 2, by TLC degradation of the acetal was observed.

Dichloroethanol/glycolaldehyde Protections

2,2-dimethoxyethyl benzoate **48**

In a nitrogen charged flame dried flask, 2,2-dimethoxyethanol (1.5g, 14.1mmol) was dissolved into 20mL of DCM at 0°C. 1.5 equivalents of pyridine (1.68g, 21.2mmol) were added to the mixture. Benzoyl chloride (2.98g, 21.2mmol) was dropwise mixed into the solution. The reaction solution was stirred overnight. After completion, the solution was acidified with NH_4Cl and diluted with DCM. The organic phase was washed 3X with NH_4Cl to remove as much pyridine as possible. This was followed with a $NaHCO_3$ wash and drying with Na_2CO_3. Concentration provided 2.4g of product (81% yield) used in the next step without further purification. Characterization corresponds to previous published results.[83]

Silyl dichloroethanols

Synthesis of TBDPS and TBS protected dichloroethanol achieved through similar method of thymidine protections (see above).

((2,2-dimethoxyethoxy)methyl)benzene **49**

In a nitrogen charged flame dried flask, 2,2-dimethoxyethanol (1.5g, 14.1mmol) was dissolved into 20mL of DCM at 0°C. 1.5 equivalents of pyridine (1.68g, 21.2mmol) were added to the mixture. Benzyl bromide (2.41g, 14.1mmol) was dropwise mixed into the solution. The reaction solution was stirred overnight. After completion, the solution was acidified with NH_4Cl and diluted with DCM. The organic phase was washed 3X with NH_4Cl to remove as much pyridine as possible. This was followed with a $NaHCO_3$ wash and drying with Na_2CO_3. Purification via flash chromatography was required to remove unreacted benzyl bromide. Concentration provided 2.6g of product (95% yield). Characterization corresponds to previously published results.[84]

((2,2-dichloroethoxy)methyl)benzene **50**

In a nitrogen charged flame dried flask, 2,2 dichloroethanol (2g, 17.4mmol) was dissolved in 35mL of DMF at 0°C. To this chilled solution, NaH (0.69g, 17.4mmol) added and allowed to stir until bubbling ceased. Benzyl bromide (5.95g, 34.8mmol) via a dropwise addition was allowed to stir until TLC showed full conversion. Reaction solution was acidified with saturated NH_4Cl and diluted with DCM. Aqueous phase was extracted twice with DCM followed by brine wash of combined organic layers. Concentration onto silica following drying with Na_2SO_4 and filtering through celite. Purification via flash chromatography with 15% EtOAc in hexane provided 3.1g (86% yield) of product. Characterization corresponds to previously published results.[85]

Glycolaldehyde Transacetalizations

A) In a nitrogen charged flame dried flask, 2 eq of protected thymidine was dissolved in MeCN (0.5M) followed by protected glycolaldehyde. Sequentially, $CoCl_2 \cdot 6H_2O$ (1 eq)

and TMSCl (1eq) and reaction monitored by TLC. After 24 hrs only a small amount ~10% silylation observed alongside unreacted starting material.

B) In a nitrogen charged flame dried flask, benzyl glycolaldehyde (1 eq) was dissolved in DCM followed by addition of TESOTf (1.1 eq) and collidine (1.5 eq). After allowing to stir for 30min, 2 eq of protected thymidine was added and reaction was stirred overnight. Reaction was acidified with NH_4Cl and the organic layer was dried over Na_2SO_4. The reaction was columned with 50% EtOAc in hexanes. Silylation of thymidine starting material observed with no other desired reactivity. Characterization agreed with previous work.

5' and 3'thymidine base promoted reactions – General Reaction Procedure

In a nitrogen charged flame dried flask, base (2.5 eq) was suspended in solvent (0.2M). Sequentially, protected thymidine (2.1 eq) and protected dichloroethanol (1 eq) were added and the reaction was warmed to the desired temperature. Reaction was allowed to proceed overnight followed by filtration of reaction mixture to remove undissolved salts. The reaction was columned with either 50% EtOAc in hexanes or 5%MeOH in methanol depending on number of protecting groups on the thymidine. In all cases, no desired product was observed.

O,S and S,S Acetal System

Synthesis of O,S Mixed Acetal

methyl 2-chloro-2-(methylthio)acetate **53**

In a nitrogen charged flame dried flask, 2-meththioxy methyl acetate (2g, 16.6mmol) and thionyl chloride (2.2g, 16.6mmol) were stirred together in DCM (20mL) at -15°C and

allowed to warm over 6hrs. The reaction mixture was concentrated directly to isolate 2.3g (90% yield) of product. Characterization corresponds to previously published results.[86]

methyl 2-((2-(((tert-butyl dimethylsilyl) oxy) methyl) -5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl)oxy)-2-(methylthio)acetate **54 2_52Bs1**

In a nitrogen charged flame dried flask, 5'-TBS thymidine (0.25g, 0.7mmol) and 2-thiomethoxy-2-chloro methyl acetate (0.14g, 0.85mmol) were dissolved in 7mL of MeCN. To this solution, silver carbonate (0.29g, 10.5mmol) was added and the reaction was refluxed overnight. The reaction mixture was filtered and purified via column chromatography to provide 0.19g (56% yield) of product. **^{1}H NMR** (300 MHz, Chloroform-d) δ 7.55 (d, J = 0.9 Hz, 0H), 6.46 (s, 1H), 6.35 (ddd, J = 7.8, 5.5, 4.5 Hz, 1H), 4.46 (d, J = 4.1 Hz, 1H), 4.03 (d, J = 2.6 Hz, 1H), 3.95 – 3.81 (m, 3H), 3.76 (s, 3H), 2.44 – 2.32 (m, 1H), 2.26 (s, 2H), 1.94 (d, J = 1.2 Hz, 3H), 0.92 (s, 7H), 0.11 (d, J = 1.8 Hz, 6H).

O,S Mixed Acetal Activation

In a nitrogen charged flame dried flask, 0.1g of O,S mixed acetal and 1.2 eq of 3',N^1-dibenzyl thymidine were dissolved in the respective solvent. Each activator was added in the listed equivalence and allowed to stir overnight. The reaction were monitored by TLC and purified by flash chromatography using 50% EtOAc in hexanes.

S,S Acetal Deprotections

A) In a nitrogen charged flame dried flask, dithiethoxy ethyl glyoxylate (1 eq) was dissolved in MeCN (0.5M). Sequentially, MeI (2.1 eq) and potassium carbonate (2.5 eq) were added and the reaction was stirred for 1hr. Following this, 5'-TBS thymidine (2.1 eq) was added and the reaction was refluxed overnight. The reaction was filtered through

celite, concentrated and purified via flash chromatography with only 5'-TBS, 3'-Me thymidine being isolated in 97% yield.

B) In a nitrogen charged flame dried flask, dithiethoxy ethyl glyoxylate (1 eq) was dissolved in THF (0.5M) along with 2.1 eq of 5'-TBS thymidine. 2 eq of NBS were added and the reaction was allowed to stir for 24 hrs. No reaction was observed by TLC and crude NMR confirmed no reaction.

C) In a nitrogen charged flame dried flask, dithiethoxy ethyl glyoxylate (1 eq) was dissolved in DMF (0.5M) along with 2.1 eq of 5'-TBS thymidine. 2 eq of Snyder's Reagent and the reaction was stirred at room temperature overnight. Deprotection of the thymidine was observed by TLC. The reaction was concentrated onto silica and flash columned to recover 86% of thymidine.

S,S Homodimer Method

5'-tosyl thymidine **55**

In a nitrogen charged flame dried flask, thymidine (3.1g, 13mmol) was dissolved in pyridine (30mL). After addition of tosyl chloride (2.5g, 13mmol), the reaction was stirred overnight. The reaction mixture was concentrated onto silica and purified via flash chromatography with 5%MeOH in DCM. 3.15g of product were isolated at 61% yield. Characterization corresponds to previously published results.[87]

5'-thioacetate thymidine **56**

In a nitrogen charged flame dried flask, 5'-Ts thymidine (0.5g, 1.4mmol) was dissolved in acetone (5mL) with 4 equivalents of potassium thioacetate (0.62g, 5.4mmol). The reaction was refluxed for 8 hrs. After conversion observed by TLC, the reaction mixture was concentrated onto silica directly. Purification by flash chromatography with 5%MeOH in

DCM provided 0.3g of product (74% yield). Characterization corresponds to previously published results.[88]

5'-thioacetate-3'-(tert-butyldimethylsilyl) thymidine **57**

In a nitrogen charged flame dried flask, 5'-thioacetate thymidine (2.2g, 12.3mmol) was dissolved in DMF (40mL) with imidazole (2.04g, 30mmol). To this solution, TBSCl (3.4g, 22.5mmol) was added and the reaction was stirred overnight at room temperature. The solution was acidified with NH_4Cl and extracted with EtOAc twice. The organic layers were dried over Na_2SO_4 and concentrated. The product was used in the next step without further purification.

5'-thio-3'-(tert-butyldimethylsilyl) thymidine **58**

In an open round bottom flask, the crude 5'-thioacetate-3'-TBS was suspended in a 1M NaOH solution in MeOH. The reaction was stirred until full conversion was observed. The solution was acidified with Amberlyst A-15 resin and purified via column chromatography using 5% MeOH in DCM. 1.26g of 5'-SH was recovered (41% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.33 (s, 1H), 6.25 (t, J = 6.7 Hz, 1H), 4.35 (d, J = 7.0 Hz, 0H), 3.94 (q, J = 4.7 Hz, 1H), 2.99 – 2.64 (m, 2H), 2.28 (dd, J = 6.7, 4.4 Hz, 1H), 2.24 – 2.11 (m, 1H), 1.94 (d, J = 1.2 Hz, 3H), 0.89 (s, 9H), 0.09 (d, J = 1.4 Hz, 6H).

Protecting Group Experimental Procedure

Screening of Alcohols

ethyl 2-(benzyloxy)-2-ethoxyacetate **58**

In a nitrogen charged flame dried flask, 2-chloro-2-ethoxy ethyl acetate (2g, 12mmol) and benzyl alcohol (2.6g, 24mmol) were combined in MeCN (45mL). Potassium carbonate (4.1g, 30mmol) was added and the heterogenous mixture was refluxed overnight. After

18hrs, the mixture was filtered through celite to remove excess potassium carbonate and was concentrated onto silica. Purification by flash chromatography provided 2.1g (74% yield) of product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 5H), 4.98 (s, 1H), 4.82 – 4.62 (m, 2H), 4.33 – 4.16 (m, 2H), 3.78 – 3.55 (m, 2H), 1.30 (t, J = 7.2 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.35, 136.98, 128.32, 127.89, 127.78, 96.66, 67.94, 62.61, 61.35, 14.92, 14.02.

ethyl 2-ethoxy-2-(4-phenylbutoxy)acetate **59**

In a nitrogen charged flame dried flask, 4-phenyl-1butanol (0.2g, 1.3mmol) and 2-chloro-2-ethoxy ethyl acetate (0.62g, 3.3mmol) were combined in MeCN (10mL). Potassium carbonate (0.46g, 3.3mmol) was added and the heterogenous mixture was refluxed overnight. After 18hrs, the mixture was filtered through celite to remove excess potassium carbonate and was concentrated onto silica. Purification by flash chromatography provided 0.34g (94% yield) of product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (dd, J = 8.2, 6.9 Hz, 2H), 7.23 – 7.12 (m, 3H), 4.90 (d, J = 10.1 Hz, 1H), 4.26 (p, J = 7.0 Hz, 3H), 3.79 – 3.56 (m, 5H), 2.65 (t, J = 7.4 Hz, 2H), 1.81 – 1.59 (m, 4H), 1.38 – 1.17 (m, 10H). **^{13}C NMR** (126 MHz, CDCl3) δ 167.41, 142.09, 128.25, 128.12, 125.57, 97.49, 97.37, 66.41, 62.36, 62.22, 61.20, 61.18, 35.45, 28.98, 27.73, 14.91, 14.89, 13.98.

ethyl 2-ethoxy-2-(naphthalen-2-yloxy)acetate **60**

In a nitrogen charged flame dried flask, 2-naphthanol (0.2g, 1.3mmol) and 2-chloro-2-ethoxy ethyl acetate (0.62g, 3.3mmol) was combined in MeCN (10mL). Potassium carbonate (0.46g, 3.3mmol) was added and the heterogenous mixture was refluxed overnight. After 18hrs, the mixture was filtered through celite to remove excess potassium

carbonate and concentrated onto silica. Purification by flash chromatography, 20% EtOAc in hexanes, provided 0.36g (94% yield) of product mixed with side product

ethyl 2-ethoxy-2-(2-(thiophen-3-yl)ethoxy)acetate **61**

In a nitrogen charged flame dried flask, 2-thiophene ethanol (0.2g, 1.6mmol) and 2-chloro-2-ethoxy ethyl acetate (0.65g, 3.9mmol) were combined in MeCN (10mL). Potassium carbonate (0.54g, 3.9mmol) was added and the heterogenous mixture was refluxed overnight. After 18hrs, the mixture was filtered through celite to remove excess potassium carbonate and was concentrated onto silica. Purification by flash chromatography provided 0.35g (85% yield) of product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.22 (dd, J = 4.9, 2.9 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.96 (d, J = 4.9 Hz, 1H), 4.35 – 4.12 (m, 3H), 3.85 – 3.75 (m, 2H), 3.70 – 3.48 (m, 4H), 2.94 (t, J = 6.9 Hz, 2H), 1.36 – 1.13 (m, 10H). **^{13}C NMR** (126 MHz, CDCl3) δ 167.41, 138.74, 128.43, 125.27, 121.40, 97.53, 97.50, 66.60, 62.63, 62.37, 61.40, 30.53, 15.05, 14.99, 14.12.

2-(1,2-diethoxy-2-oxoethoxy)ethyl acrylate **62**

In a nitrogen charged flame dried flask, 2-hydroxyethyl acrylate (0.2g, 1.7mmol) and 2-chloro-2-ethoxy ethyl acetate (0.65, 3.9mmol) were combined in MeCN (10mL). Potassium carbonate (0.54g, 3.9mmol) was added and the heterogenous mixture was refluxed overnight. After 18hrs, the mixture was filtered through celite to remove excess potassium carbonate and was concentrated onto silica. Purification by flash chromatography provided 0.17g (41% yield) of product. **^{1}H NMR** (500 MHz,$CDCl_3$) δ 5.91 (dddd, J = 17.2, 10.4, 6.0, 5.4 Hz, 1H), 5.30 (dd, J = 17.2, 1.6 Hz, 1H), 5.19 (dd, J = 10.4, 1.4 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.14 (ddt, J = 10.1, 6.0, 1.4 Hz, 2H), 3.76 –

3.55 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.41, 133.53, 117.73, 96.70, 67.23, 62.45, 61.38, 14.96, 14.05.

Stability Screening

Each time point was reacted separately in an open glass test tube. 0.15g of the mixed acetal was dissolved into 3mL of the respective solvent system. 1 eq of either H_2SO_4 or $BF_3 \cdot H_2O$ was added and allowed to react for the requisite time period. The reaction was diluted with distilled water and DCM in equal volume. After separation the organic layer was dried over Na_2SO_4 and concentrated down. Crude NMRs are presented in the body of the chapter.

GNA and isoGNA Experimental Procedures

Monomer Synthesis

1,3-dityrityl glycerol **63**

Glycerol (4g, 43.4mmol) was suspended in DCM at room temperature. 2eq of trityl chloride (23.9g, 86.8mmol) was added along with 7eq of pyridine (24g, 304mmol) and catalytic DMAP (0.53g, 4.3mmol). Mixture was stirred overnight and quenched with NH_4Cl. After extracting the aqueous phase twice with DCM, the combined organic layers were washed with $NaCO_3$ and brine. The organic layer was dried with $NaSO_4$, filtered through celite and concentrated to provide the title compound in 95% yield. Characterization corresponds to previously published results.[89]

N^1-benzoyl thymine **64**

Thymine (2g, 15.9mmol) was dissolved in 30mL of a 1:2 mixture of pyridine: acetonitrile. Benzoyl chloride (4.5g, 31.8mmol) was added dropwise at 0°C. The reaction was warmed to room temperature for several hours until full consumption was observed by TLC. Then

the acetonitrile was removed by rotary evaporation and the resulting mixture was dissolved in ethyl acetate and brine. The aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed with brine and $NaCO_3$ followed by drying with $MgSO_4$. After concentration onto silica it was isolated by flash chromatography with 2%MeOH in DCM in 82% yield. Characterization corresponds to previously published results.[90]

1,3-ditrityl-2-(N^1-benzoyl thymine) glycerol **65**

Ditrityl glycerol (5g, 8.7mmol) was dissolved in a mixture of 1,4 dioxane and THF (60mL:15mL). benzoyl thymine (3.9g, 17.4mmol) and triphenylphosphine (5.7g, 21.7mmol) were added to the solution. Slowly, DEAD (3.8g, 21.7mmol) was added dropwise. The reaction was stirred overnight. After completion, reaction was concentrated to remove volatiles. The crude mixture was resuspended in DCM and washed with brine 2X. The organic layer was dried with $MgSO_4$ and concentrated onto silica. Title compound was isolated via flash chromatography with 30% EtOAc in hexane. Characterization corresponds to previously published results.[91]

2-thymine glycerol **66**

Deprotection of 2-thymine glycerol was achieved through a two-step process. First the benzoyl protecting group was removed through treatment with 7N ammonia in MeOH for 4 hrs. The mixture was then acidified with 80% AcOH to a pH of 3 and stirred until full conversion was observed. Alternatively, treatment with A-15 amberlyst resin can perform the deprotection and be removed easily via filtration. Characterization corresponds to previously published results.[92]

2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)oxirane **67**

2-methoxy oxirane (2.0mL, 30mmol) was dissolved in DCM (68mL). After triethylamine (10.8mL, 81.4mmol), DMTrCl (12.9g, 38mmol) was slowly added. Reaction completed after 12 hrs. The solution was quenched and washed with $NaCO_3$ followed by drying by $NaSO_4$. Filtration through celite and concentration provided 6.5g of product at 72% yield. Characterization corresponds to previously published results.[93]

1-(3-(bis(4-methoxyphenyl)(phenyl)methoxy)-2-hydroxypropyl)-5-methylpyrimidine-2,4(1H,3H)-dione **68**

Thymine (0.71g, 5.5mmol) was dissolved in DMF (11mL) and NaH (0.047g, 1.1mmol) was added. The resulting solution was stirred at room temperature for 2 hrs. Protected oxirane (2g, 5.3mmol) was added and the reaction was refluxed overnight. The Reaction mixture was concentrated onto silica and purified via flash chromatography with 5% MeOH in DCM to provide 1.2g at 46% yield. Characterization corresponds to previously published results.[94]

1-(2,3-dihydroxypropyl)-5-methylpyrimidine-2,4(1H,3H)-dione **69**

Protected monomer (1.2g, 2.4mmol) was dissolved in DCM (10mL) and trifluoroacetic acid (0.54g, 4.8mmol). Reaction was followed by TLC and washed with $NaCO_3$ to provide the final product upon concentration. Characterization corresponds to previously published results.[95]

Keto-Acid Sugar Experimental Procedure

Model System Synthesis

ethyl 2,2-bis(ethylthio)acetate **70**

In a nitrogen charged flame dried flask, ethyl glyoxylate (3g, 29.4mmol) and $BF_3 \cdot Et_2O$ (2.1g, 14.7mmol) were dissolved in 34mL of thioethanol. The reaction was stirred

overnight and majority of thioethanol was removed by rotary evaporation. The residual residue was dissolved into Et_2O and washed with brine. Drying by $MgSO_4$ and concentration of organic phase provided quantitative yield of product (6.1g). Characterization corresponds to previously published results.[96]

ethyl 2,2-bis(ethylthio)pent-4-ynoate **71**

In a nitrogen charged flame dried flask, 2,2-dithioethyl ethyl acetate (1.5g, 7.2mmol) was dissolved in THF (8mL) and cool to 0°C. Potassium *tert*-butoxide (0.81g, 7.2mmol) was added as 1M solution in THF. After 30min of stirring, 2-bromo propyne (1.1g, 7.2mmol) was added and the reaction was stirred overnight. The reaction was acidified with NH_4Cl and diluted with DCM. The aqueous phase was extracted with DCM and the combined organic layers were dried with Na_2SO_4 and filtered through celite. The concentrated product was used in the next step without further purification (0.96g, 54% yield). Characterization corresponds to previously published results.[97]

ethyl 2,2-bis(ethylthio)-6-hydroxy-6-phenylhex-4-ynoate **72**

In a nitrogen charged flame dried flask, alkyne (0.46g, 1.9mmol) was dissolved in THF (15mL) at -78°C. LHMDS (0.32g, 1.9mmol) as a 1M solution in THF was added to the chilled mixture and stirred for 30min to allow for full deprotonation. At which time, benzaldehyde (0.2g, 1.9mmol) was dropwise added to the solution and the reaction was stirred for ~6hrs. After completion by TLC, the solution was warmed to room temperature and acidified with saturated NH_4Cl and diluted with DCM. The aqueous phase was extracted twice with DCM and dried with Na_2SO_4. After filtering through celite, the solution was concentrated onto silica and purified via flash chromatography. 30%EtOAc in hexane provided the product in 48% yield (0.32g). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61

– 7.49 (m, 1H), 7.44 – 7.27 (m, 3H), 5.44 (d, J = 1.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 1H), 3.01 (s, 1H), 2.69 (q, J = 7.5 Hz, 3H), 1.24 (q, J = 7.4 Hz, 6H). **^{13}C NMR** (75 MHz, cdcl3) δ 169.52, 140.75, 128.41, 128.18, 126.78, 83.13, 81.98, 64.61, 63.11, 62.39, 28.82, 24.39, 14.04, 13.64.

ethyl 2,2-bis(ethylthio)-6-hydroxy-6-phenylhexanoate **73**

In a nitrogen charged flame dried flask, alkyne (0.2g, 0.5mmol) was dissolved in methanol (15mL) and ~0.2g of 10% Pd/C was added to the solution. Nitrogen in the flask was evacuated and hydrogen gas was introduced through two balloons. The reaction was stirred for 48hrs with new balloons added after 24hrs. After completion, filtering of the reaction mixture removed Pd/C and the crude mixture was purified by flash chromatography with 10% EtOAc in hexanes. 0.12g (6% yield) of product was isolated cleanly, more was contaminated with side product but were included in next step.

5-(3-benzyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(benzyloxy)tetrahydrofuran-2-carbaldehyde **74**

In a nitrogen charged flame dried flask, DMSO (1.2 eq) was dissolved in DCM (0.3M) at -78°C. To this solution, 3,N^1-dibenzyl thymidine (2g, 4.7mmol) was added and stirred at this temperature for 3 hrs. After which time, 4 eq of TEA were added and the reaction was warmed to room temperature over an hr. The reaction mixture was washed twice with brine and the aqueous phase was extracted once with DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated to 0.79g (40%yield). Characterization corresponds to previously published results.[98]

5' Aldehyde Reactions and Control

In a nitrogen charged flame dried flask, 1.2 eq of the terminal alkyne was dissolved in the listed conditions (0.2M). 1.2 eq of requisite base was added and the reaction was stirred for 30 min. 0.1g of the aldehyde (thymidine or adenosine) was added and the reaction was monitored by TLC. Denucleosidation was observed by TLC. This was confirmed after acidification of the reaction mixture with NH_4Cl and extraction into EtOAc. The control reaction was performed with the same conditions only without the alkyne.

Model Hydrogenation

ethyl (Z)-2,2-bis(ethylthio)-6-hydroxy-6-phenylhex-4-enoate **74**

In a nitrogen charged flame dried flask, Alkyne (0.15g, 0.4mmol) was dissolved in MeOH (15mL). Approximately 0.1g of PtO_2 was added. The nitrogen was pumped out and two hydrogen gas balloons were inserted to charge the flask with hydrogen. Reaction was allowed to stir for 24 hrs. After which, the solution was filtered to remove the PtO_2 and concentrated. The crude mixture was used in the next step without further purification.

ethyl 2-hydroxy-6-phenyl-3,6-dihydro-2H-pyran-2-carboxylate **75**

In a nitrogen charged flame dried flask, hexenoate (0.05g, 0.15mmol) was dissolved in DCM (2mL) and silver triflate (0.072g, 0.3mmol) was added. The reaction was stirred at room temperature overnight. The reaction mixture was filtered through celite and concentrated. A 1:4 mixture of H2O: DMSO (5mL) was used to suspend the mixture and was heated to 75°C for 1hr. Solution was partitioned between sodium bicarbonate and EtOAc. Aqueous phase was extracted twice with EtOAc. The organic phase was dried over Na2SO4, filtered and purified via column chromatography. Using 20%EtOAc in hexanes, 0.021g (60% yield) was isolated. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 – 7.36 (m, 5H), 6.33 (d, J = 1.1 Hz, 1H), 5.51 (dd, J = 13.7, 3.7 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.93

(dd, J = 17.1, 13.7 Hz, 1H), 2.75 (ddd, J = 17.0, 3.7, 1.1 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 128.88, 126.26, 109.96, 88.34, 85.80, 81.45, 63.99, 55.52, 26.33, 24.67.

Transacetalization of Model System

In a nitrogen charged flame dried flask, 0.1g of pyren (1 eq) was dissolved in DCM (0.5M) at room temperature followed by 2 eq of 5'-TBS thymidine. To this solution, 1 eq of the respective lewis acid was added and the reaction was monitored by TLC. $SnCl_4$, and TMSOTf resulted in baseline decomposition. $BF_3{\cdot}Et_2O$ and $HfOTf_4$ led to clean deprotection to thymidine while a dry down of the solution with MgCl at 85°C for 3 days resulted in no reaction. Only pTSA resulted in a trace amount of product by crude NMR but it could not be replicated or scaled up.

Ribose System

4-hydroxy-4-((3aR,4R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)but-2-yn-1-yl 4-methylbenzenesulfonate **76**

In a nitrogen charged flame dried flask, protected ribose (2g, 9.8mmol) was dissolved in MeCN (25mL) with IBX (5.5g, 19.5mmol) and refluxed overnight. The reaction mixture was filtered and concentrated. The crude mixture was portioned out for the next step without further purification. 0.2g (0.98mmol) of ribose aldehyde was dissolved in toluene with $ZnOTf_2$ (0.34g, 0.98mmol) and TEA (0.2g, 1.9mmol) at room temperature. The reaction was stirred overnight. After completion, the reaction was acidified with NH_4Cl and extracted twice with EtOAc. The organic layers were dried with Na_2SO_4 and filtered through celite. Purification via flash chromatography 50% EtOAc in hexanes provided 0.28g (68% yield) of product.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 8.6, 0.4 Hz, 2H), 7.40 – 7.31 (m, 2H), 4.93 (d, J = 0.5 Hz, 2H), 4.64 – 4.48 (m, 4H), 4.31 (tdd, J = 7.3, 1.0, 0.4 Hz, 2H), 4.01 (dd, J = 7.2, 1.4 Hz, 3H), 3.23 (s, 4H), 2.45 (s, 1H), 1.45 (s, 2H), 1.28 (d, J = 0.7 Hz, 4H).

4-((tert-butyldiphenylsilyl)oxy)-4-((3aR,4S,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)but-2-yn-1-yl 4-methylbenzenesulfonate **77**

In a nitrogen charged flame dried flask, OTs-Alkyne (0.25g, 0.6mmol) was dissolved in DCM (5mL) with TBDPSCl (0.25g, 0.9mmol) and imidazole (0.06g, 0.9mmol) at room temperature and reacted overnight. The reaction mixture was acidified with NH_4Cl and extracted twice with EtOAc. The solution was purified via flash chromatography 30% EtOAc in hexanes to provide 0.22g (55% yield) of product.

Thiane Substitution

In a nitrogen charged flame dried flask. 1eq of the desired ribose alkyne was dissolved in THF (0.2M) with 1.5eq of dithiane ethyl glyoxylate. To this solution, 1.5eq of KOtBu as a 1M solution in THF was added and the reaction was monitored by TLC to determine decomposition. If decomposition was not fully observed, the reaction was acidified with NH_4Cl and extracted twice with EtOAc. Crude NMR used to determine results.

Fluoride Substitution

1-phenyl-3-(trimethylsilyl)prop-2-yn-1-ol **79**

In a nitrogen charged flame dried flask, TMS-acetylene (3.3g, 33.9mmol) was dissolved in THF and cooled to -78°C. To this solution, nBuLi (2.2g, 33.9mmol) as a 1.7M solution in hexanes was added and stirred for 30min. Benzaldehyde (3g, 28.3mmol) added in 2 portions and the reaction was monitored by TLC. Full conversion achieved after 5 hrs. The solution was acidified with NH_4Cl and diluted into ethyl acetate. The aqueous phase

was extracted twice with ethyl acetate and dried with Na_2SO_4. After filtering through celite, the product was purified by flash chromatography in 20% EtOAc in hexanes at quantitative yield (5.7g). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 1H), 7.35 (d, J = 5.6 Hz, 4H), 5.44 (s, 1H), 4.64 (dd, J = 7.4, 6.0 Hz, 1H), 1.92 – 1.65 (m, 0H), 1.33 (dd, J = 7.4, 6.6 Hz, 1H), 0.97 – 0.79 (m, 2H), 0.22 (s, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.91, 128.57, 128.40, 127.46, 126.76, 125.93, 74.68, 64.90, 38.79, 27.99, 22.62, 14.04, -0.15.

(3-(benzyloxy)-3-phenylprop-1-yn-1-yl)trimethylsilane **80**

In a nitrogen charged flame dried flask, TMS-alkyne (2g, 9.8mmol) was dissolved in THF (30mL) and cooled to 0°C. NaH (0.23g, 9.8mmol) was added and the reaction was stirred until bubbling ceased. Benzyl bromide (1.6g, 9.8mmol) was added and stirred overnight. The reaction was acidified with NH_4Cl and diluted with DCM. The aqueous phase was extracted with DCM and the combined organic layers were washed with brine and dried over Na_2SO_4. After filtering through celite, the product was purified via flash chromatography with 10% EtOAc in hexanes. 1.6g (57% yield) of product was isolated. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 – 7.49 (m, 1H), 7.46 – 7.36 (m, 4H), 7.27 – 7.16 (m, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.26 (d, J = 11.3 Hz, 1H), 3.42 (d, J = 12.9 Hz, 1H), 3.19 (d, J = 12.9 Hz, 1H), 1.40 – 1.26 (m, 2H), 1.03 – 0.82 (m, 3H), 0.38 – 0.17 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.04, 138.96, 136.05, 131.26, 128.23, 128.08, 127.63, 127.22, 126.92, 104.19, 95.09, 80.93, 66.98, 51.42, 31.66, 22.72, 14.20, -0.09.

Bromo-pyruvate Test Reactions

TMS Alkyne – In a nitrogen charged flame dried flask, TMS-alkyne (1 eq) was dissolved in THF (0.2M) at room temperature. To this solution either TBAF (1.5 eq as a 1M solution in THF), CsF (1.5 eq), or TASF (1.5 eq) was added, followed 30min later by bromo

methylpryruvate (1.5 eq) and the reaction was stirred overnight. CsF, after 18hrs, showed no reactivity with starting material fully recovered after filtering off of CsF salt. TBAF and TASF treatment resulted in cleavage of the TMS group at near quantitive yield but no substitution with bromo methyl pyruvate.

Alkyne – In a nitrogen charged flame dried flask, the model alkyne (1 eq) was dissolved in THF (0.2M) at 0°C followed by addition of LHMDS (1.5 eq) as a 1M solution in THF. The solution was stirred for 30min. At which point, bromo methyl pyruvate (1.5 eq) was added and the reaction was stirred at room temperature overnight. The reaction mixture was acidified with NH_4Cl and extracted twice with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated. Crude NMR indicated that addition to the carbonyl had occurred. Mass of the crude mixture showed a yield of 61%.

Oxidation Attempts

(3aR,4R,6aR)-4-(1-(benzyloxy)prop-2-yn-1-yl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole **81**

In a nitrogen charged flame dried flask, ribose alkyne (0.5g, 2.2mmol) was dissolved in THF (25mL) at 0°C. NaH (0.096g, 2.4mmol) was added and the solution was stirred until bubbling ceased. Slowly to the solution, benzyl bromide (0.69g, 4.6mmol) was added and the reaction was warmed overnight. After 18hrs, the reaction was acidified with NH_4Cl and diluted with DCM. The aqueous phase was extracted twice with DCM and the combined organic layers were dried over Na_2SO_4. The product was purified via flash chromatography (30% EtOAc in hexanes) at 55% yield (0.41g) as a 2:3 mixture of diastereomers. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.92 (s, 1H), 4.81 (dd, J = 6.0, 1.6 Hz, 1H), 4.75 – 4.66 (m, 3H), 4.57 – 4.51 (m, 4H), 4.34 (dd, J = 8.2, 2.2 Hz, 1H), 4.25

(dd, J = 9.0, 2.1 Hz, 1H), 4.21 – 4.16 (m, 1H), 4.12 (dd, J = 9.0, 1.0 Hz, 1H), 3.62 (dd, J = 10.2, 5.7 Hz, 1H), 3.55 – 3.50 (m, 1H), 3.37 (s, 3H), 3.36 (s, 2H), 1.49 – 1.43 (m, 8H), 1.31 (d, J = 0.8 Hz, 6H), 0.90 (d, J = 9.5 Hz, 28H), 0.15 (dd, J = 20.0, 1.3 Hz, 11H), 0.05 (s, 8H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 112.48, 112.39, 112.12, 109.85, 109.76, 109.32, 90.71, 89.05, 87.07, 85.14, 84.95, 84.91, 83.52, 82.22, 81.90, 81.76, 81.47, 75.02, 73.79, 65.09, 63.82, 63.73, 55.47, 55.26, 54.74, 26.61, 26.50, 26.45, 25.84, 25.70, 25.68, 25.66, 25.62, 25.22, 25.20, 25.01, 18.25, -4.30, -4.96, -5.37, -5.43.

methyl 6-(benzyloxy) -2-hydroxy -6-((3aR,4R,6aR) -6-methoxy-2,2-dimethyl tetrahydrofuro [3,4-d] [1,3]dioxol-4-yl)hex-4-ynoate **82**

In a nitrogen charged flame dried flask, above (0.44g, 1.3mmol) was dissolved in THF (25mL) and cooled to 0°C. To this solution, LHMDS (0.23g, 1.4mmol) as a 1M solution in THF was added to the mixture and stirred for 30min. After stirring, epoxide (0.27g, 2.6mmol) was added and warmed to room temperature overnight. The reaction was acidified with NH_4Cl and diluted with ethyl acetate. Aqueous phase was extracted twice with ethyl acetate and dried with Na_2SO_4. After filtration through celite, the target compound was purified via flash chromatography using 30% EtOAc in hexane at 58% yield (0.33g) as a 2:3 mixture of diastereomers. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.00 (s, 1H), 4.97 (d, J = 6.3 Hz, 1H), 4.69 (dd, J = 6.0, 0.9 Hz, 4H), 4.55 (d, J = 6.0 Hz, 4H), 4.41 (dd, J = 9.4, 1.2 Hz, 1H), 4.19 (ddd, J = 9.0, 5.6, 1.0 Hz, 4H), 3.62 (dd, J = 10.2, 5.7 Hz, 3H), 3.52 (dd, J = 10.2, 9.0 Hz, 4H), 3.39 (d, J = 11.3 Hz, 4H), 3.36 (s, 2H), 3.29 (s, 10H), 1.47 (s, 12H), 1.32 (s, 11H), 0.89 (s, 27H), 0.06 (s, 19H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 183.60, 112.13, 110.09, 109.86, 109.81, 109.34, 88.21, 88.18, 87.08, 85.16, 85.03, 84.75,

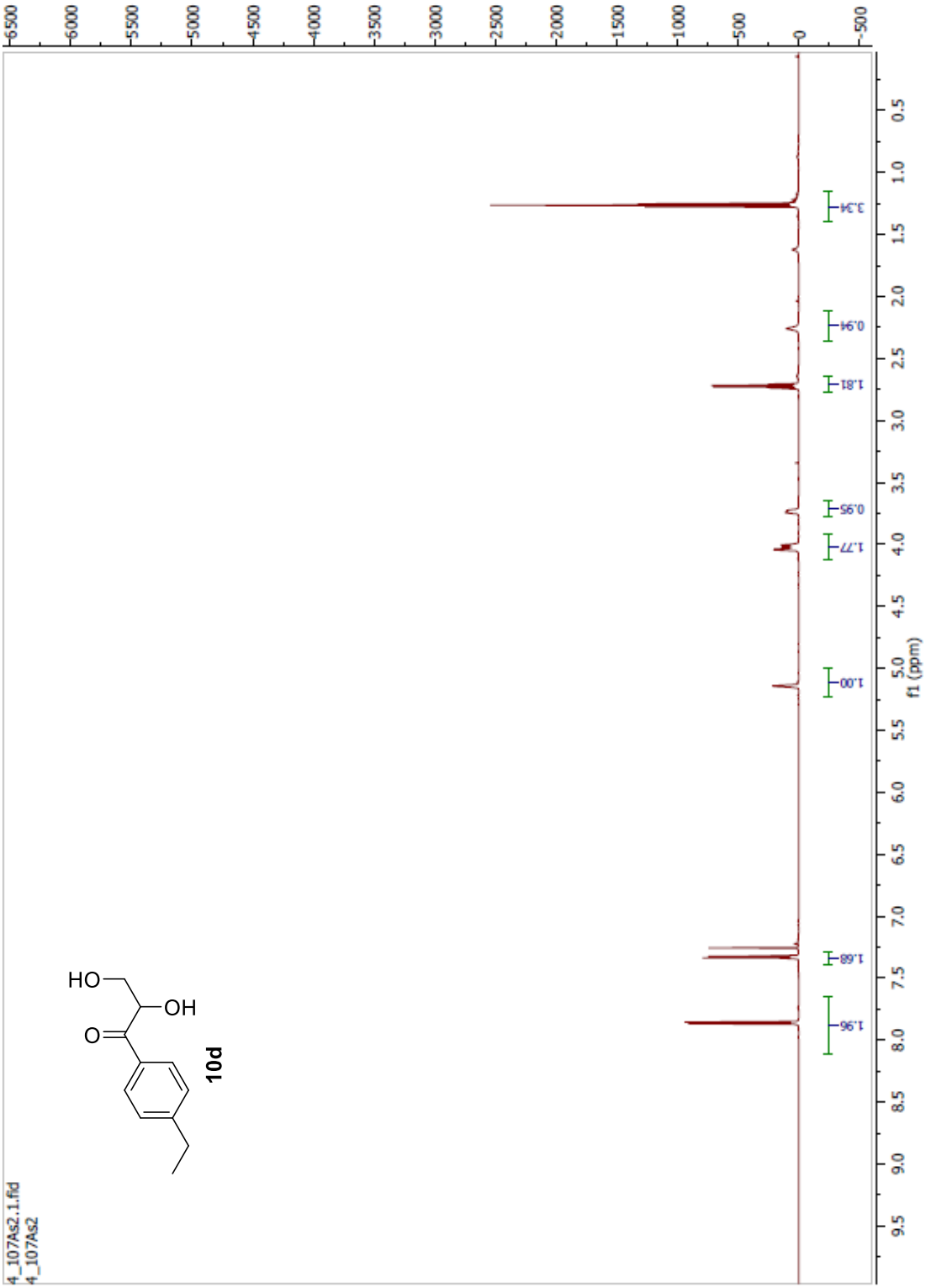
84.72, 81.91, 81.86, 81.81, 64.10, 63.74, 55.67, 54.74, 34.63, 31.56, 26.45, 26.43, 25.84, 25.62, 25.60, 25.57, 25.24, 25.01, 22.62, 18.25, 14.08, -4.41, -5.03, -5.37, -5.44.

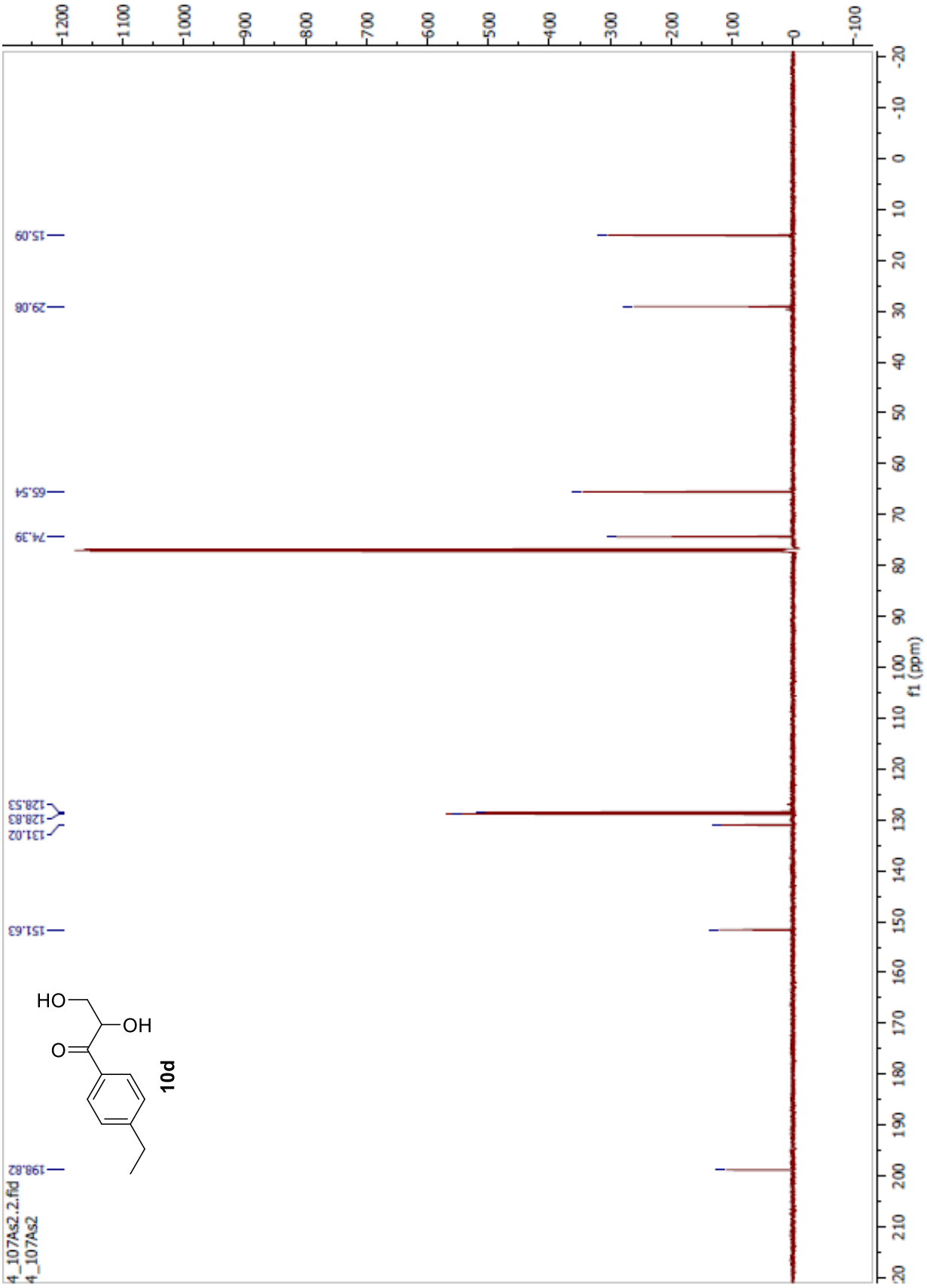
Oxidation Attempts

Swern – In a nitrogen charged flame dried flask, DMSO (1.5 eq) was dissolved in DCM (0.5M) and cooled to -78°C to which oxalyl chloride (1.1 eq) was added and the reaction bubbled vigorously then was stirred for 20min. After which, the homopropargyl alkyne (1 eq) was added and the reaction was warmed to 0°C. After 6hrs of reaction, triethylamine was added and the reaction was warmed to room temperature. TLC of the reaction showed full degradation of the starting alkyne to baseline decomposition products. Crude TLC indicated no formation of the desired product.

IBX, DMP, PDC – In a nitrogen charged flame dried flask, the homopropargyl alkyne (1 eq) was dissolved in MeCN (0.2M). 1.5 eq of the respective oxidant was added and the reaction was refluxed until conversion of the alkyne was observed or 24hrs past. In the case of IBX and DMP decomposition was observed whereas PDC showed minimal decomposition but no other products being formed by TLC. Crude NMR confirmed these observations.

Spectra of Novel Compounds

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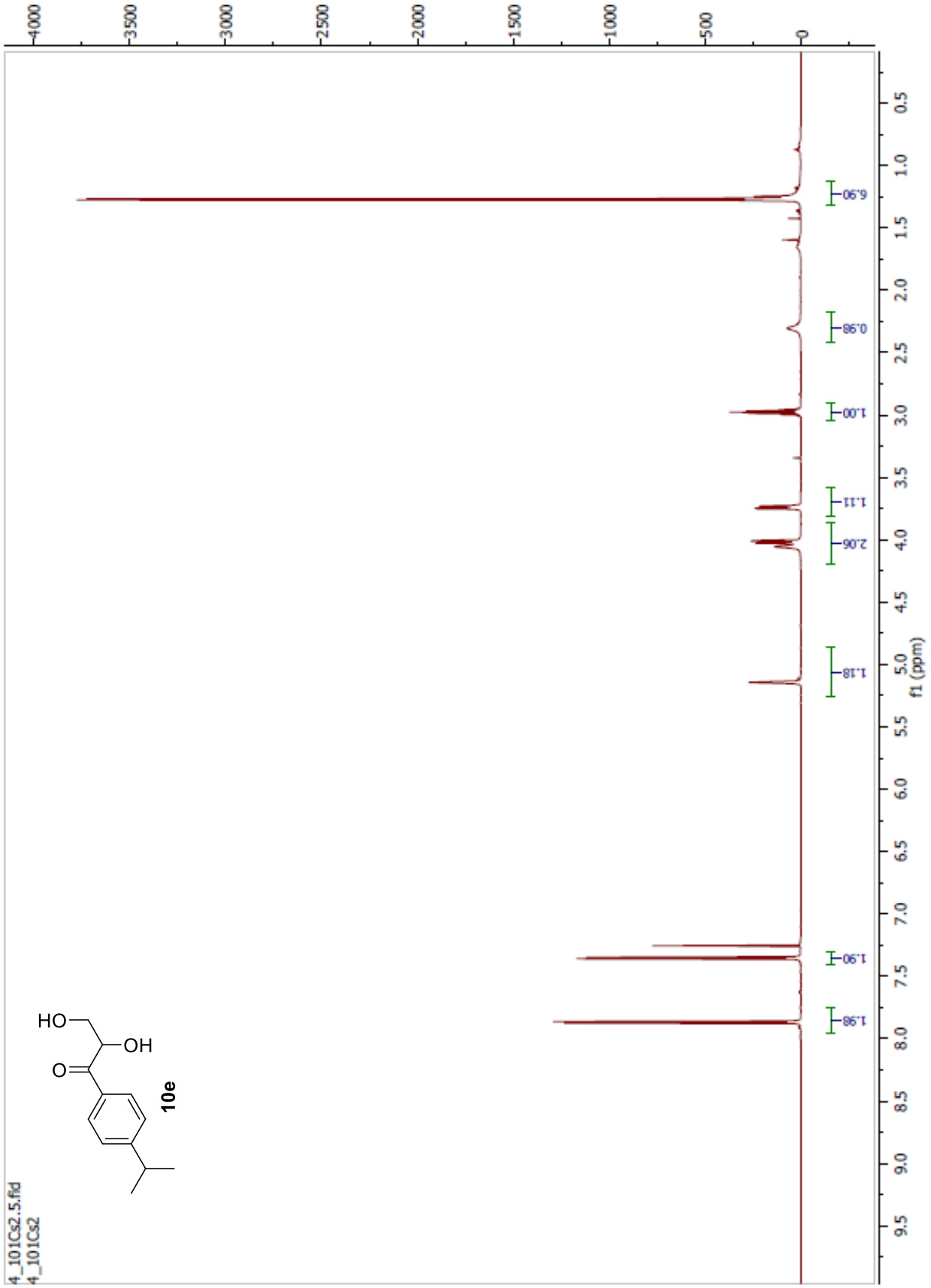
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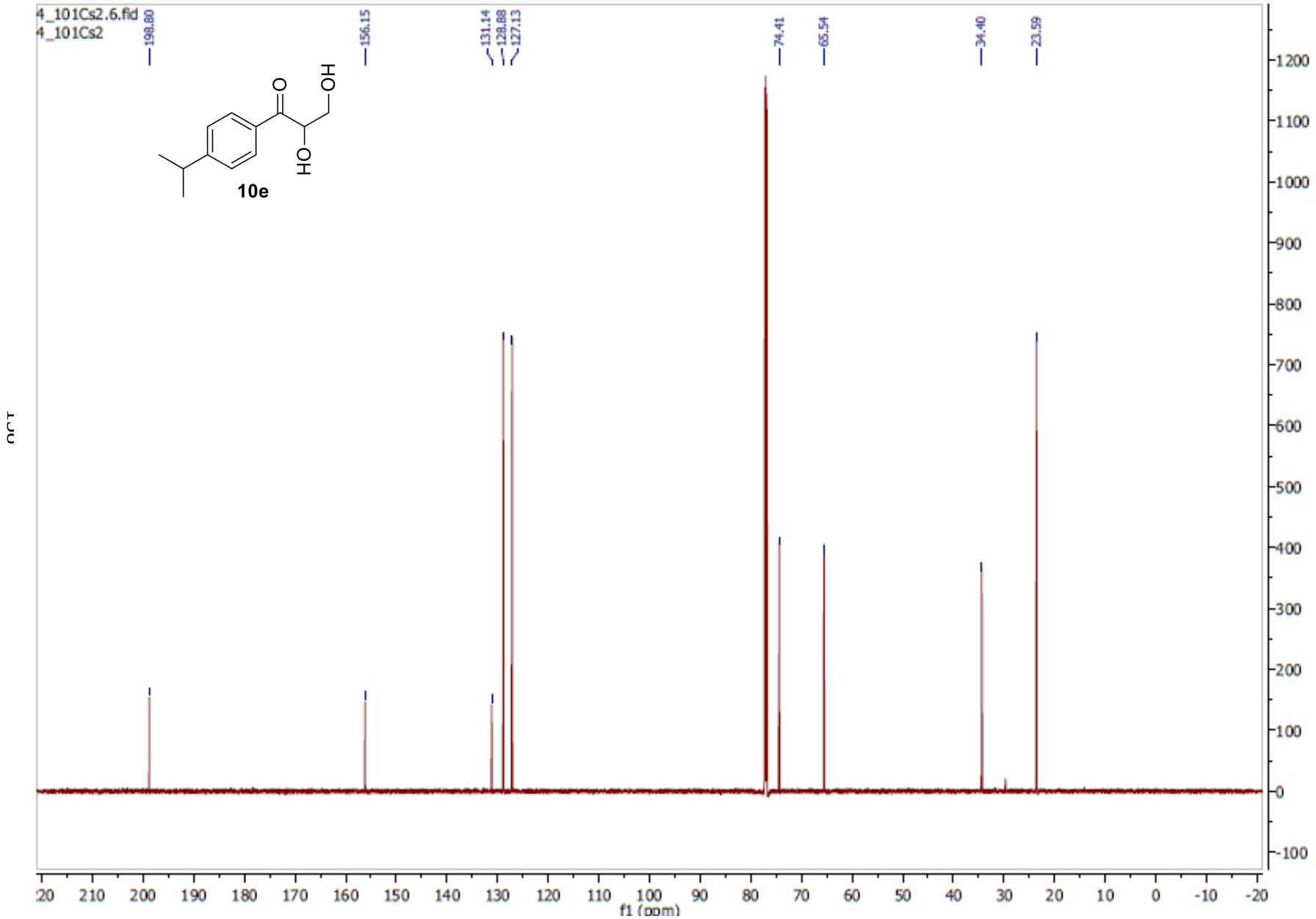
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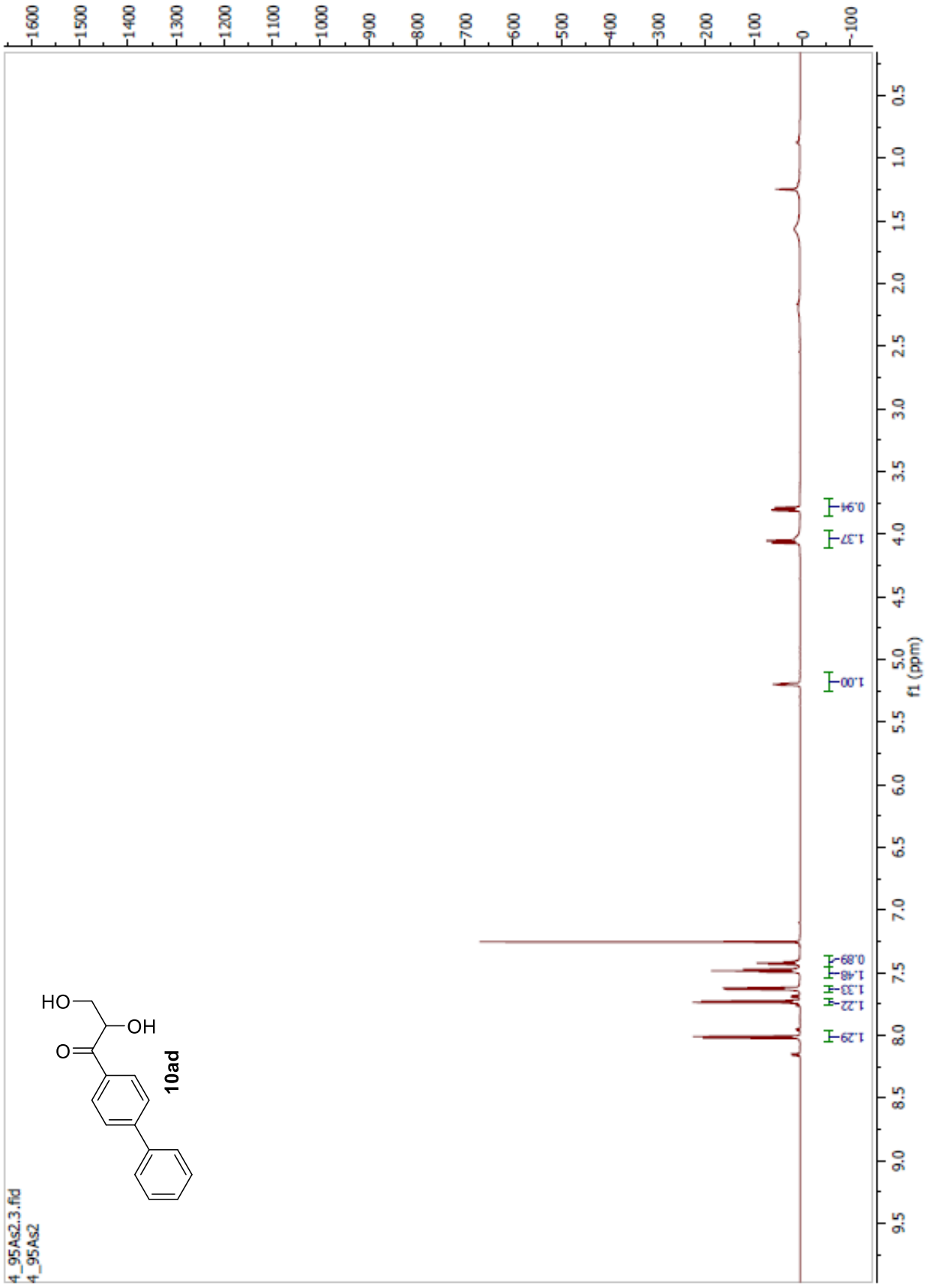
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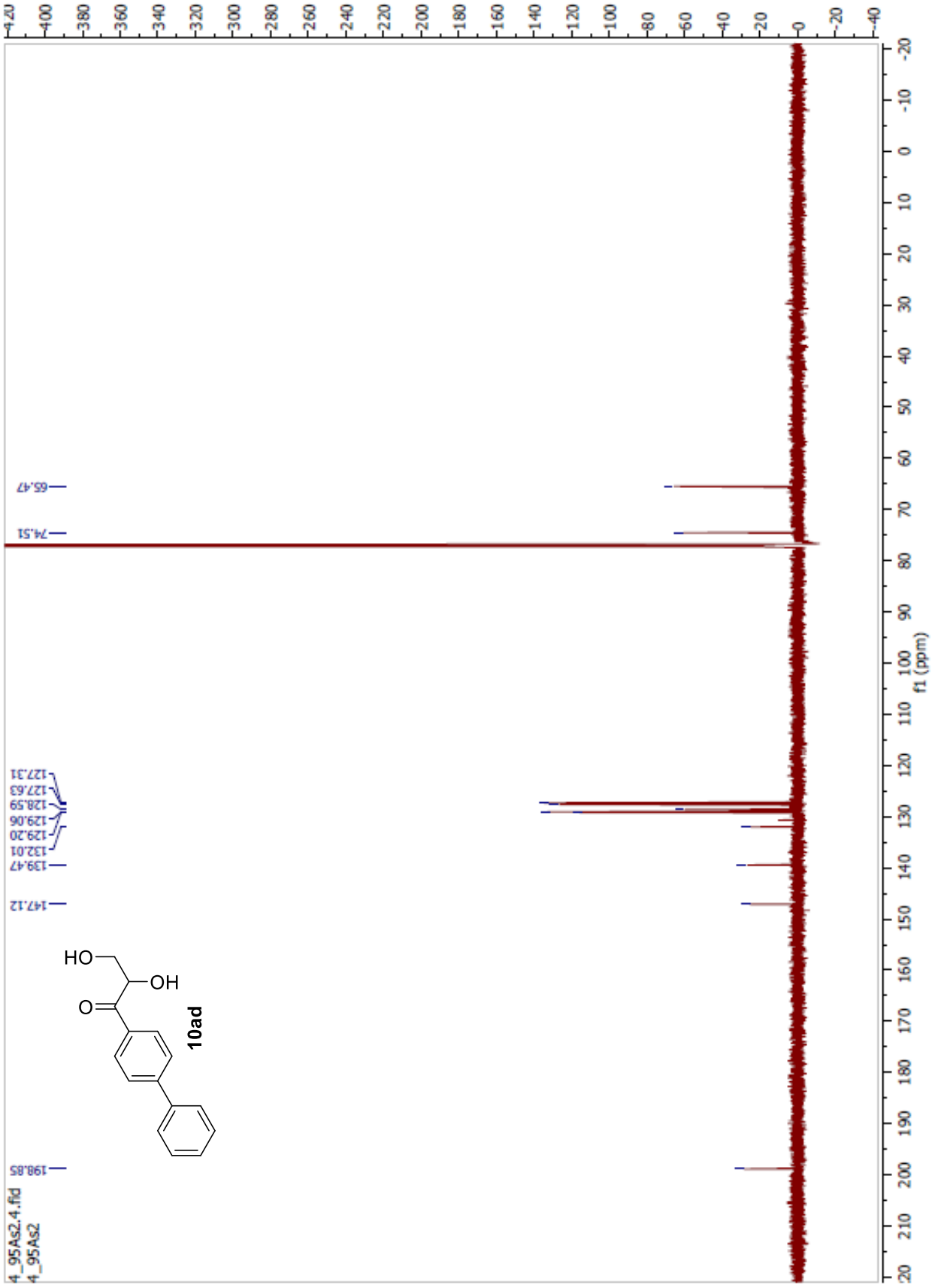
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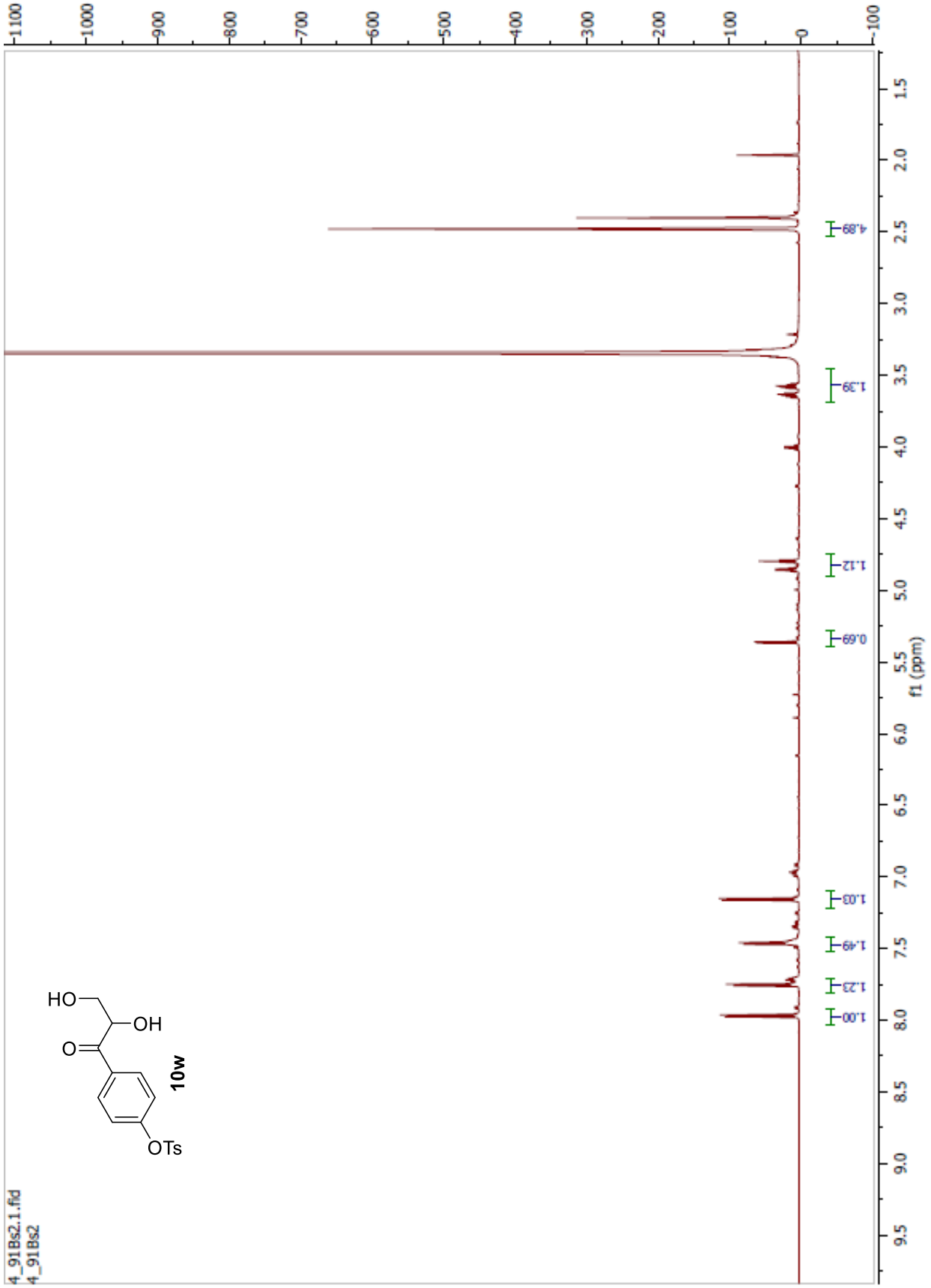
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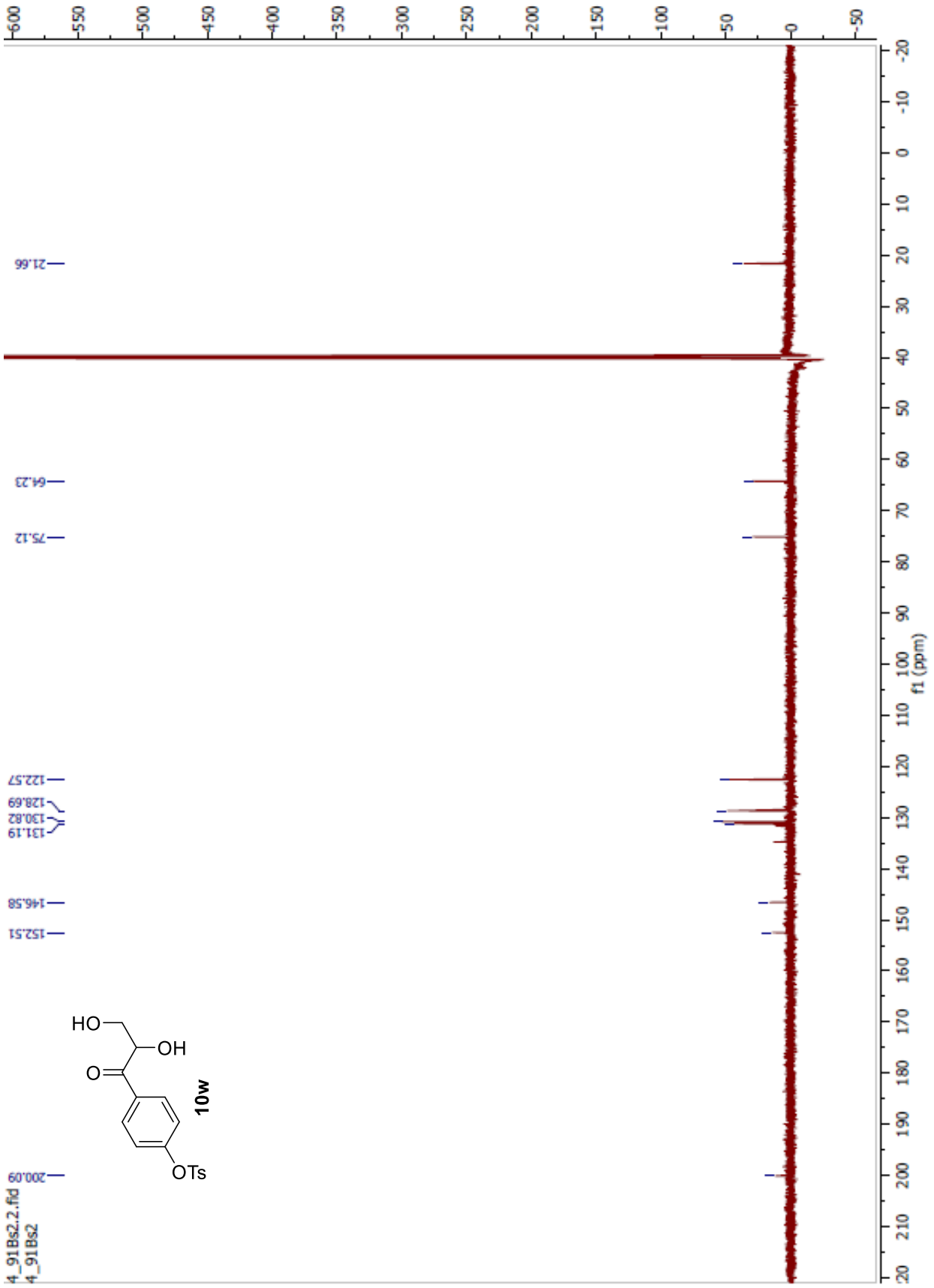
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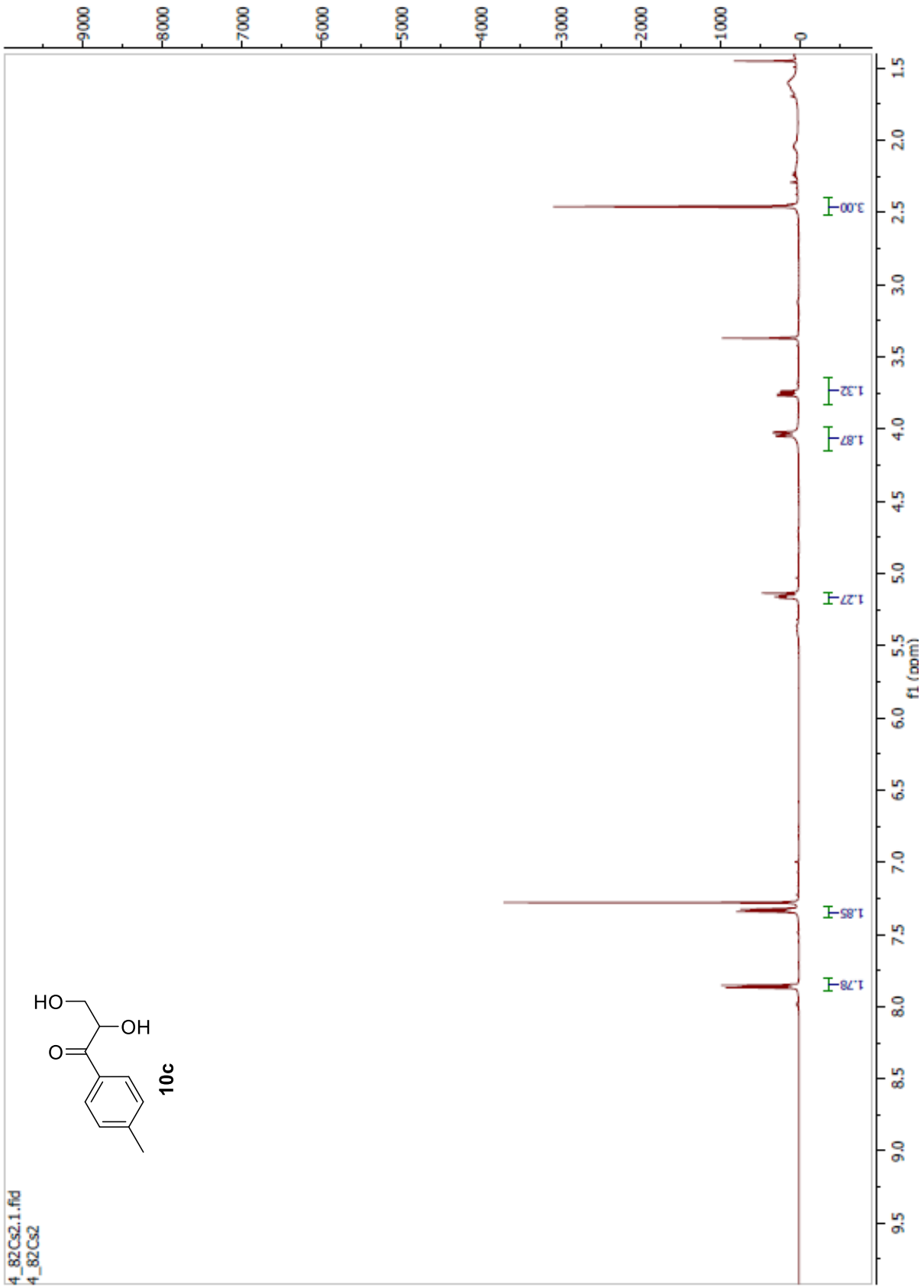
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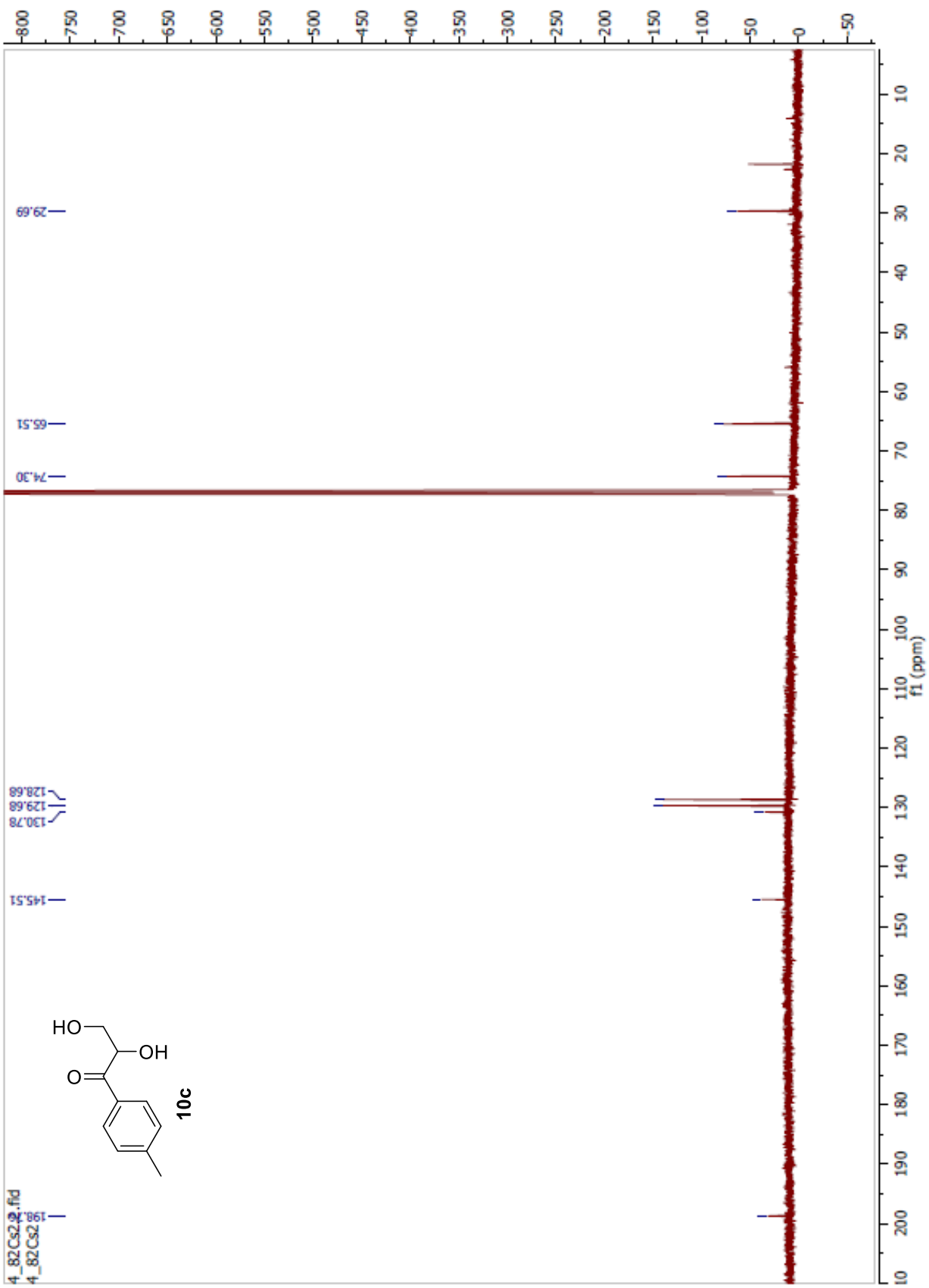
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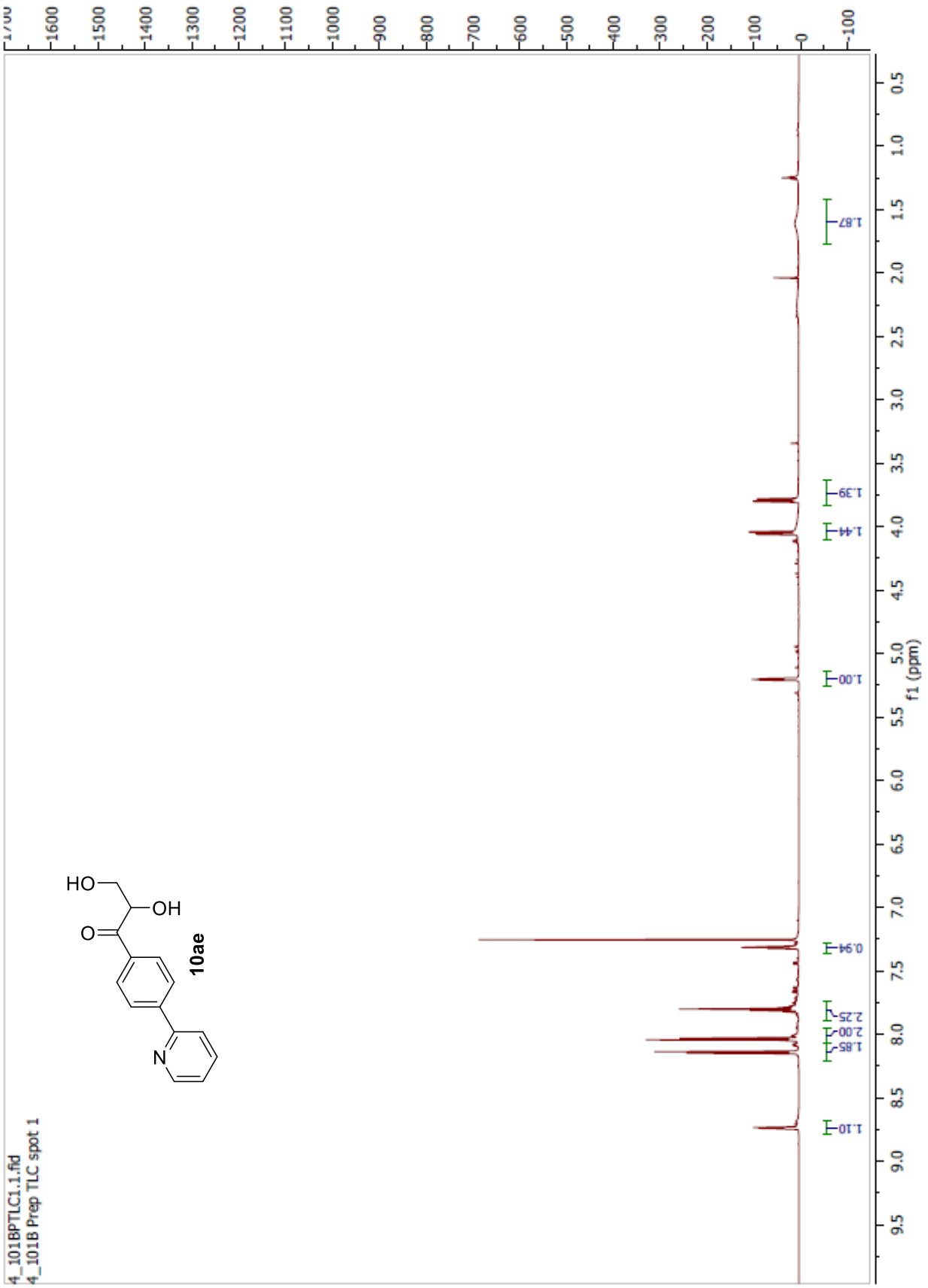
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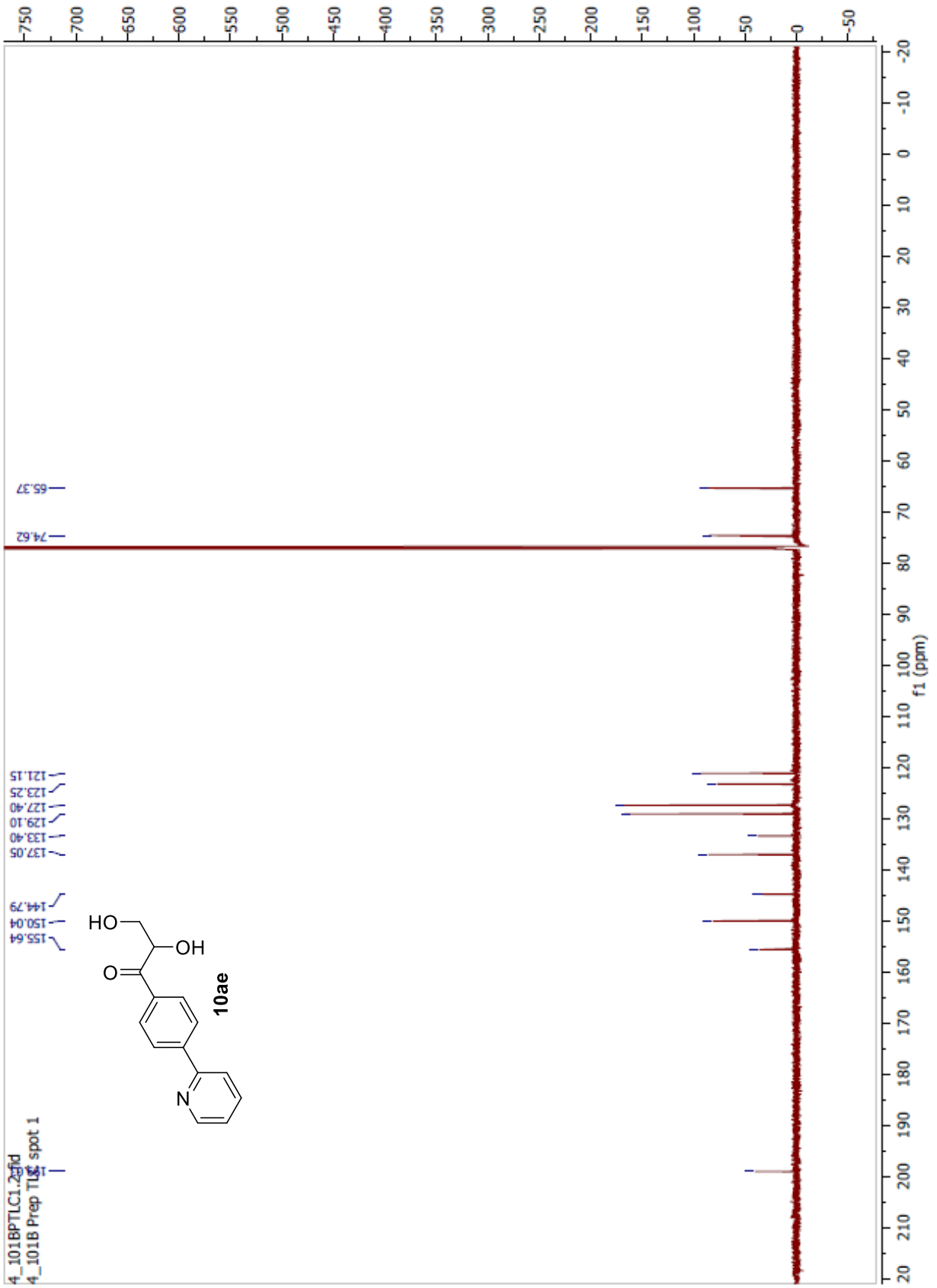
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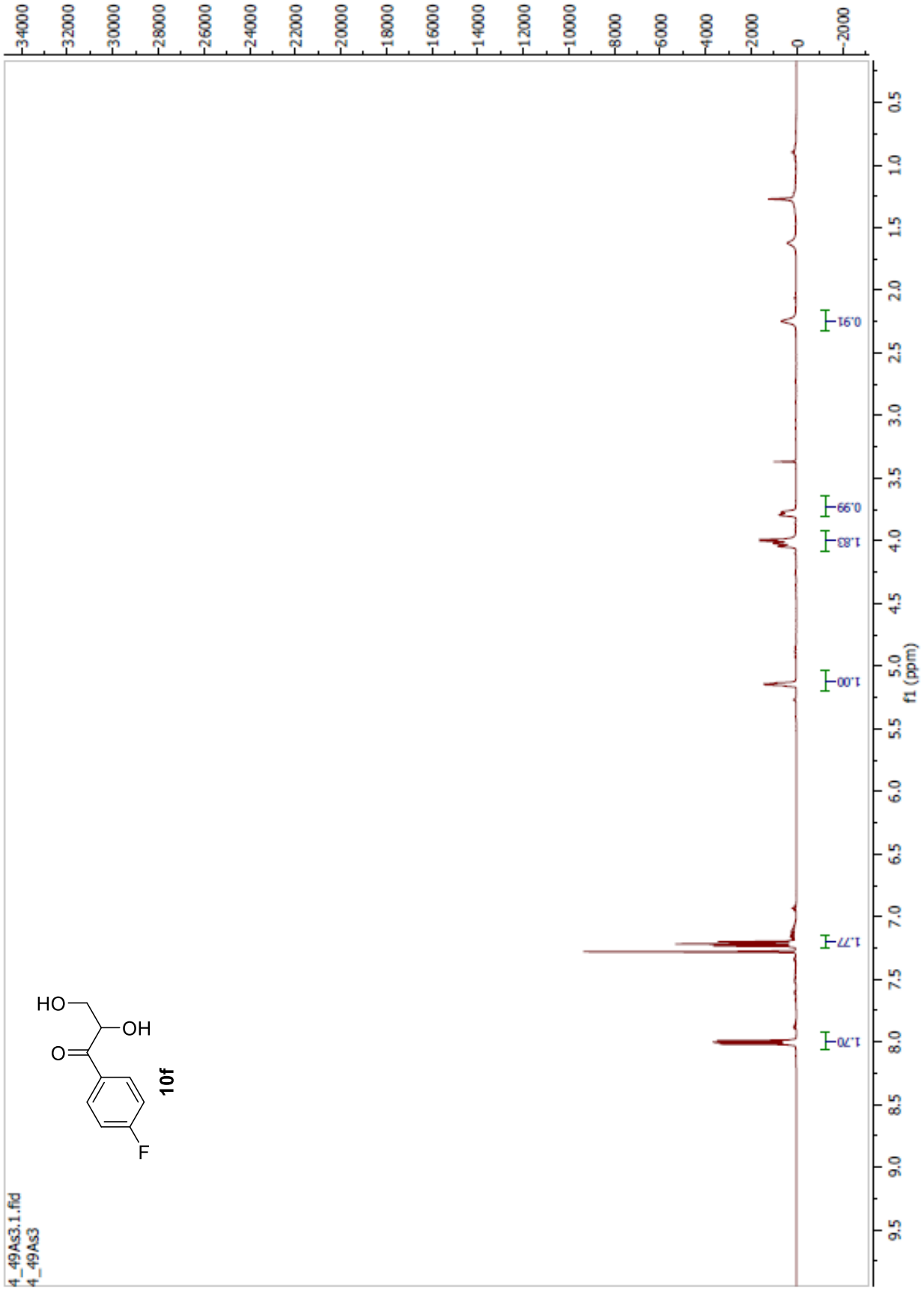
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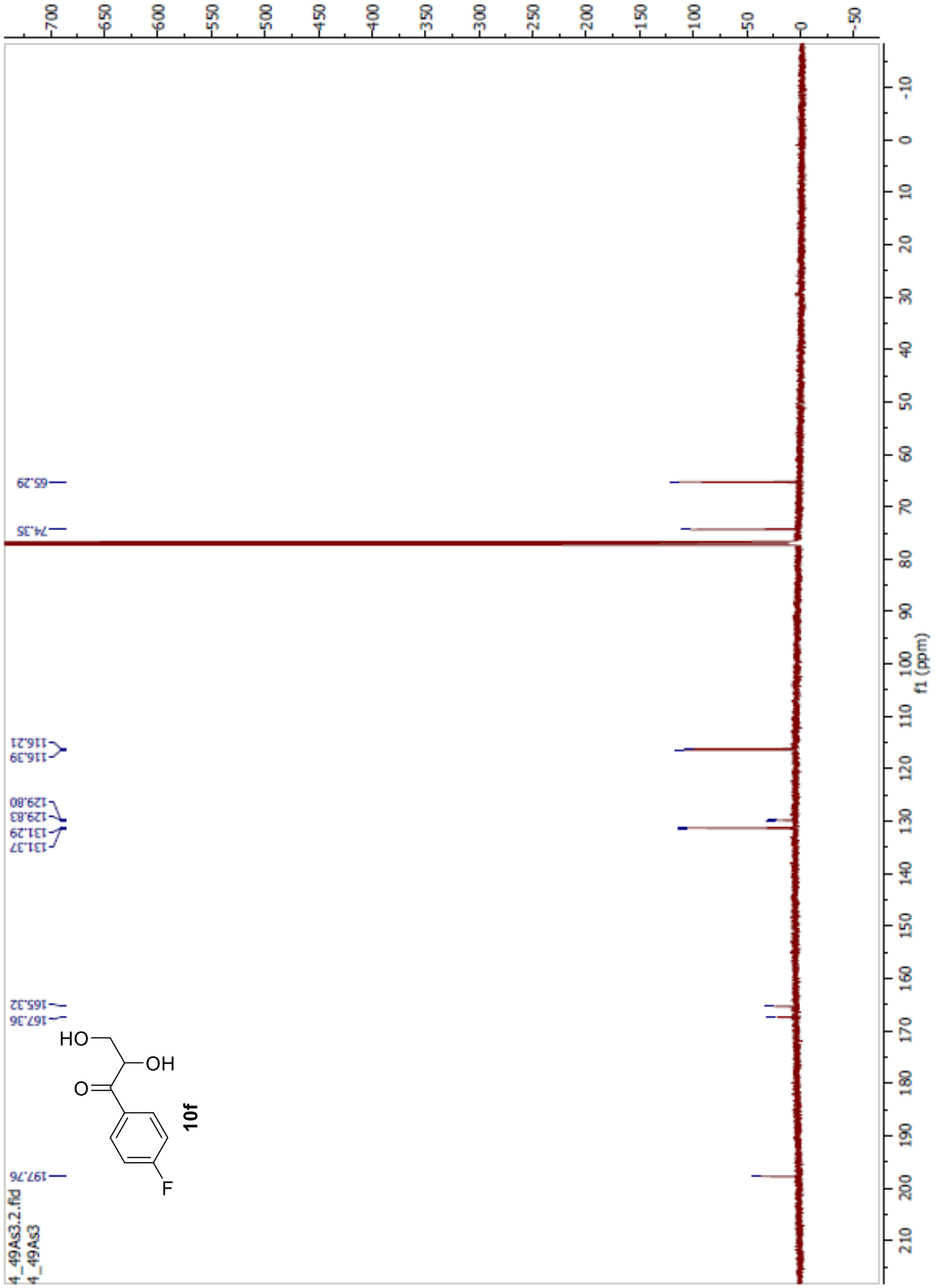
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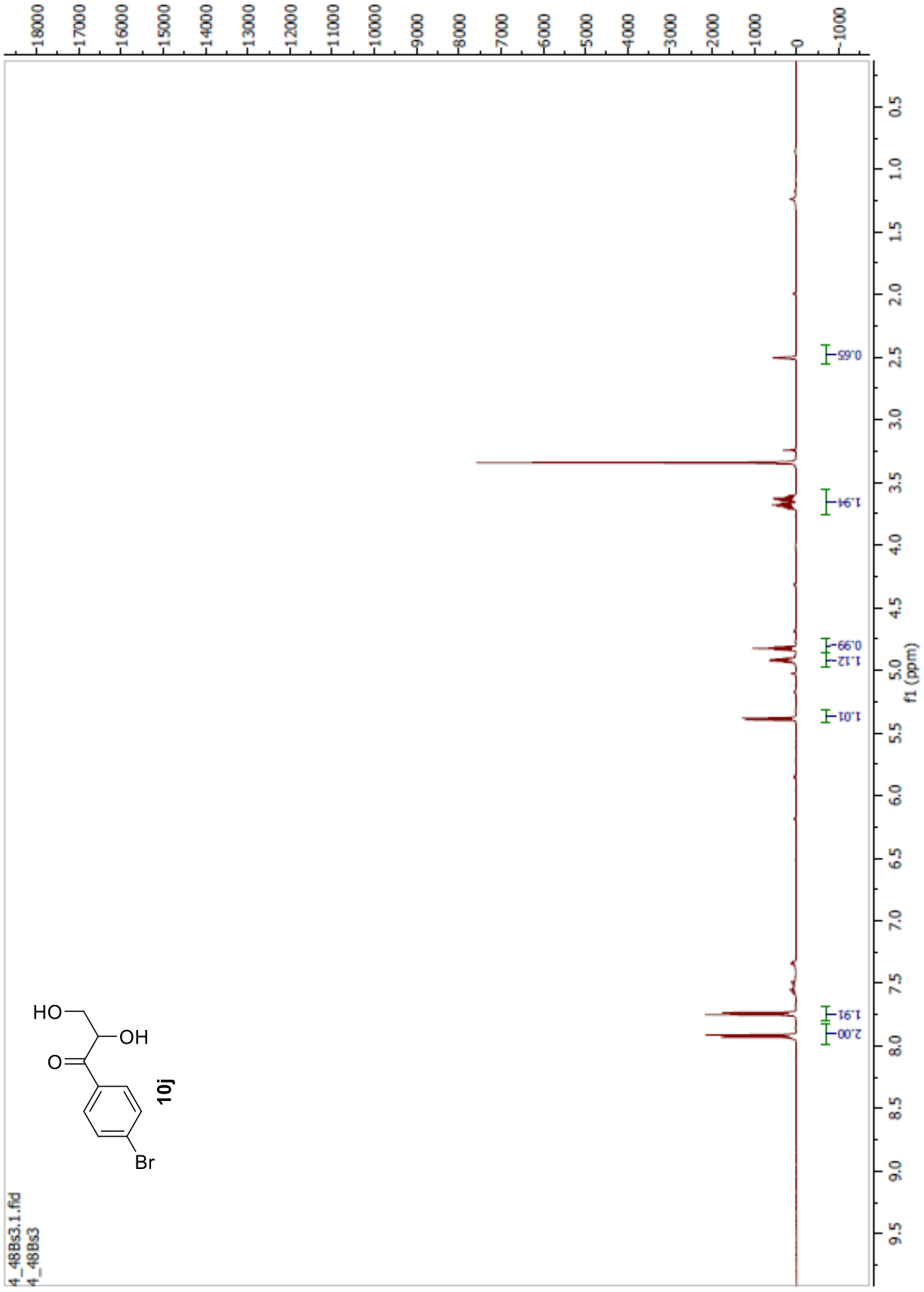
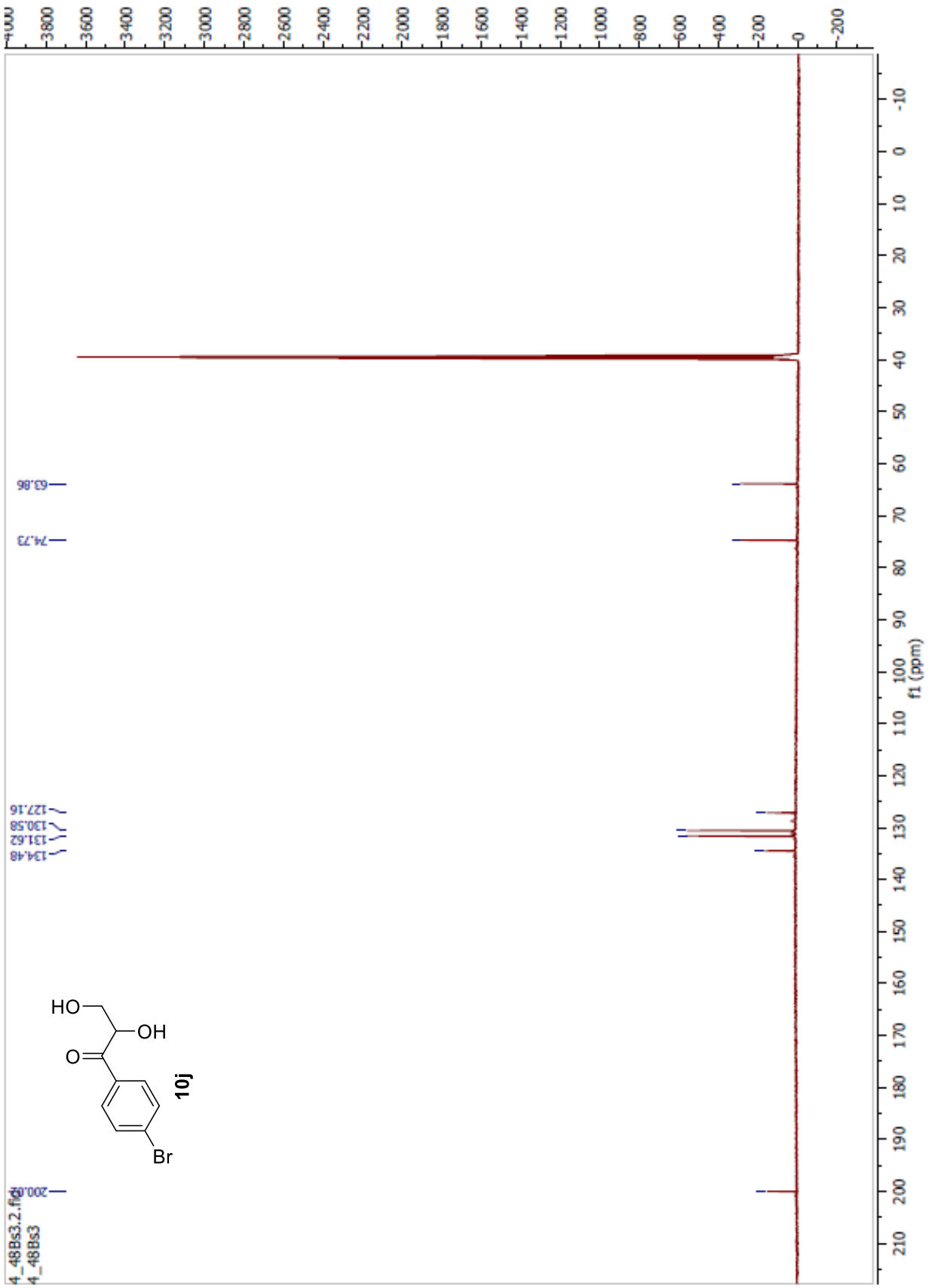
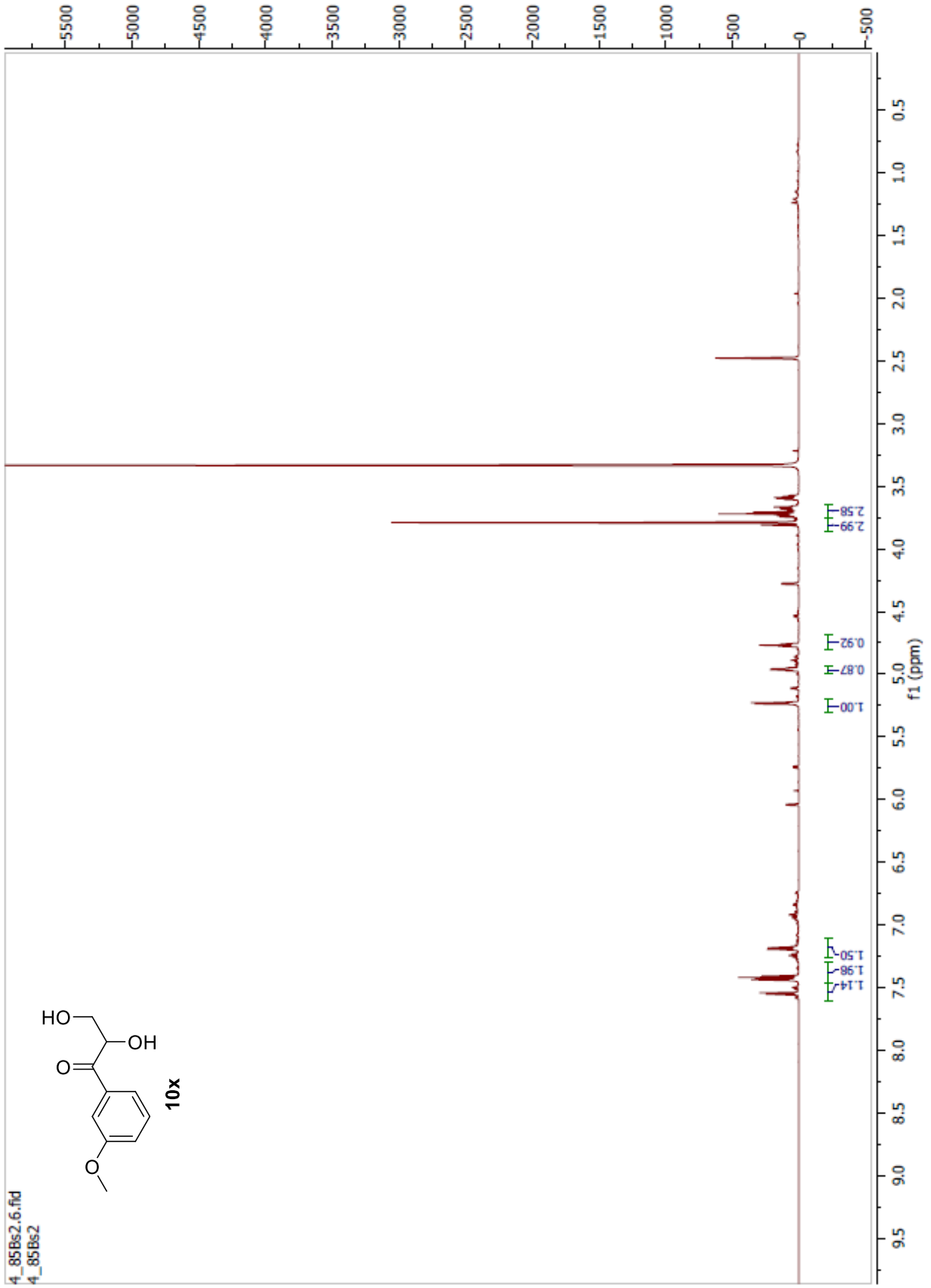
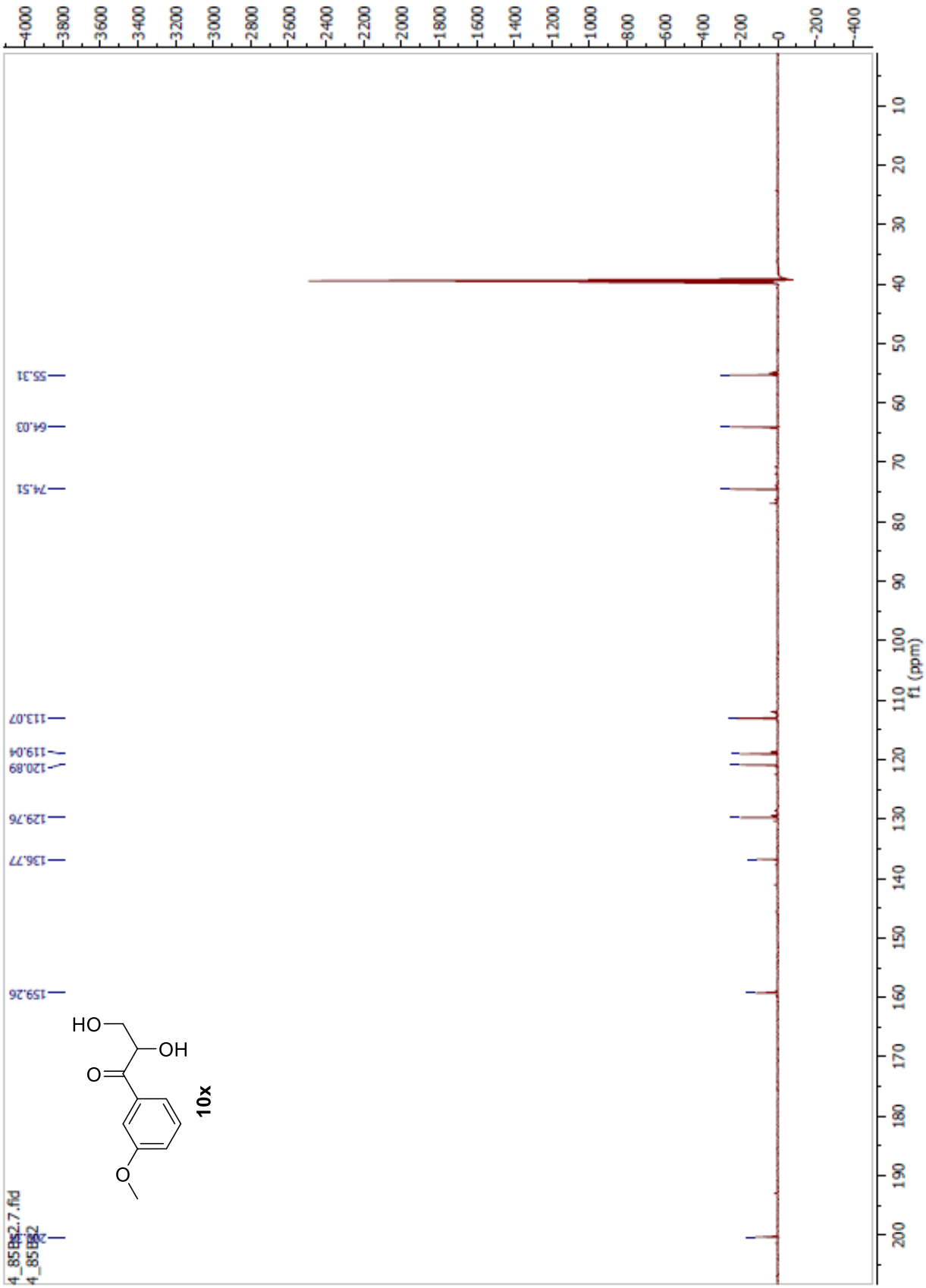
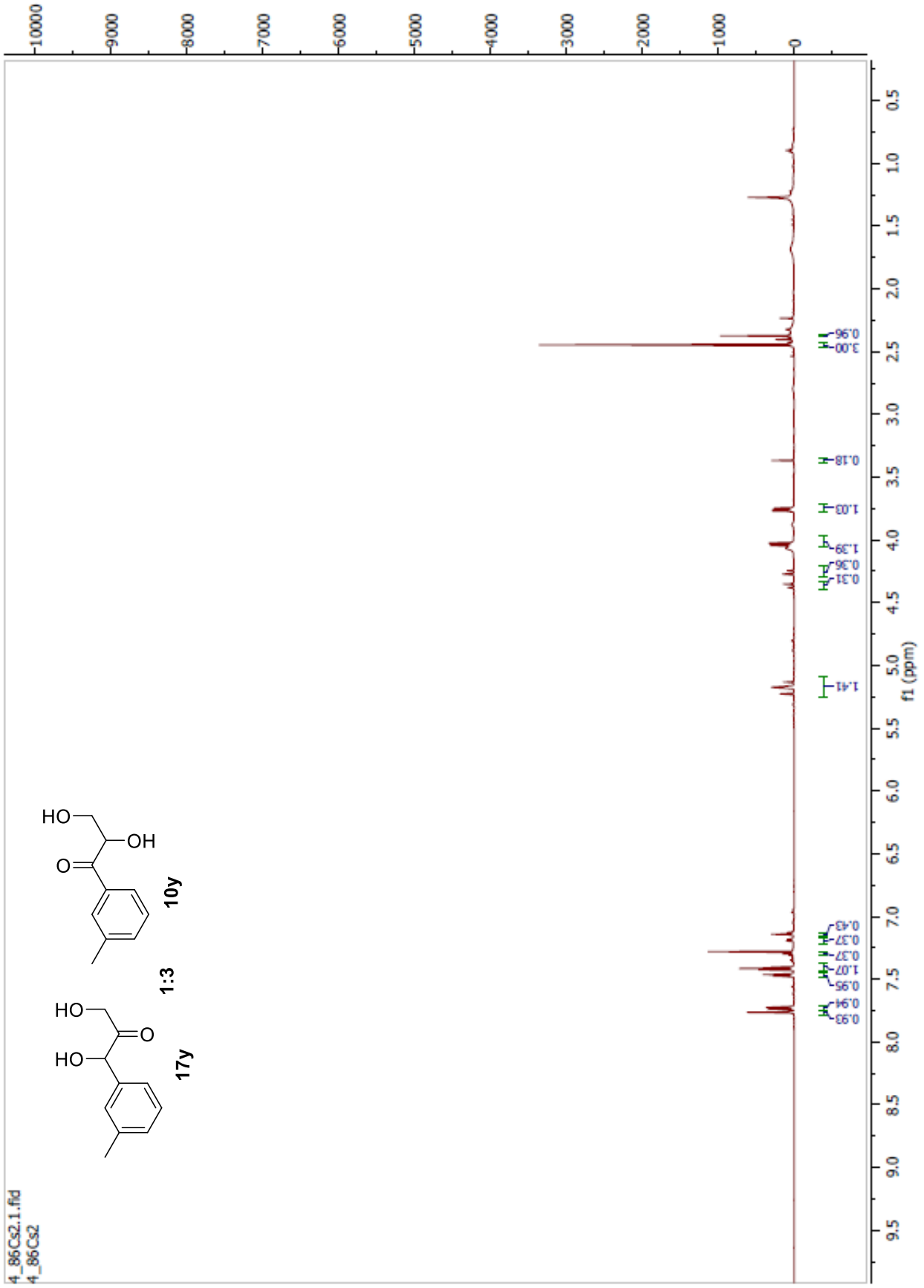
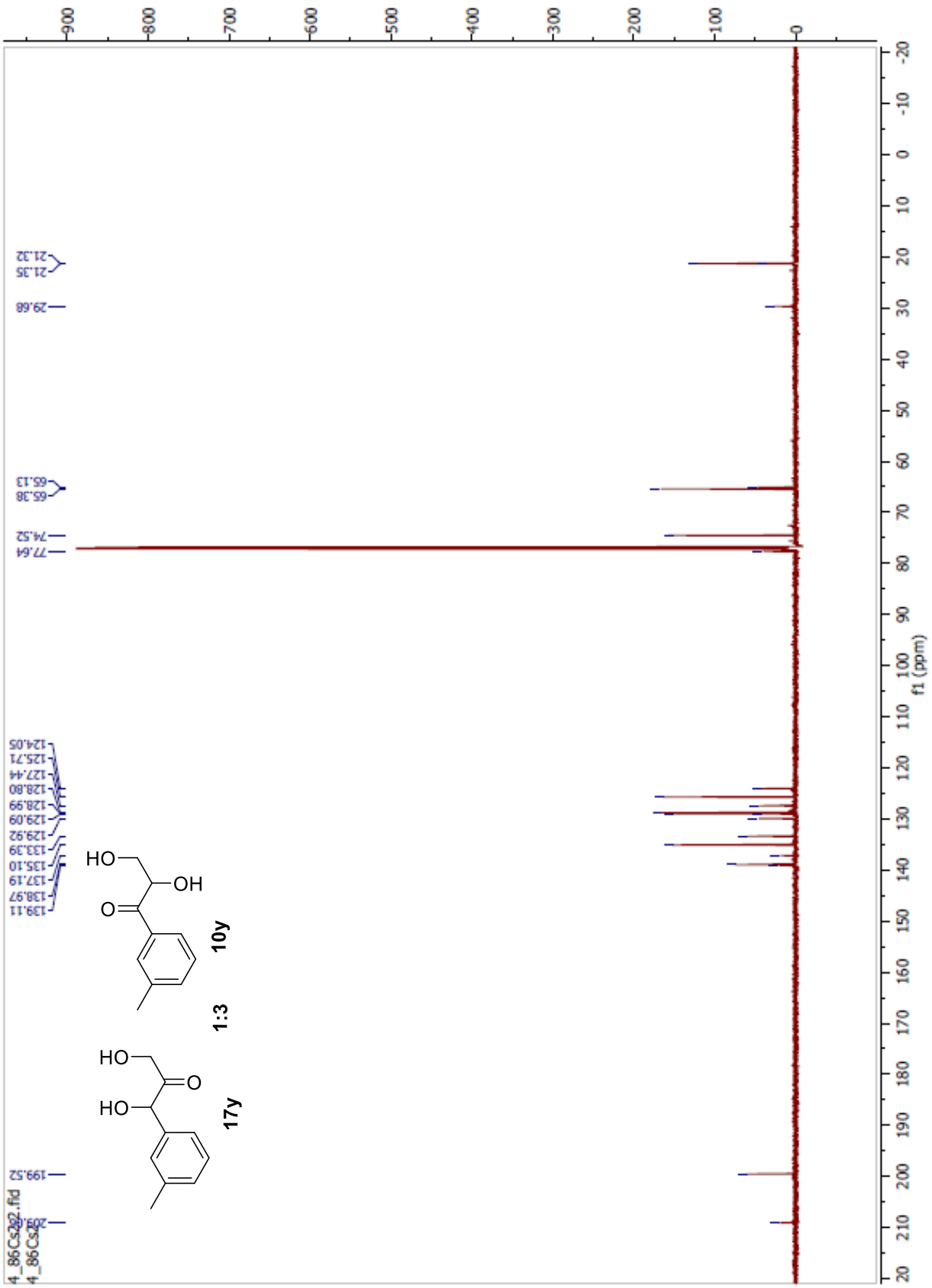

HO
OH
O
Br
10j
4_48Bs3.1.fid
4_48Bs3
0.65
1.94
0.99
1.12
1.01
1.91
2.00
f1 (ppm)

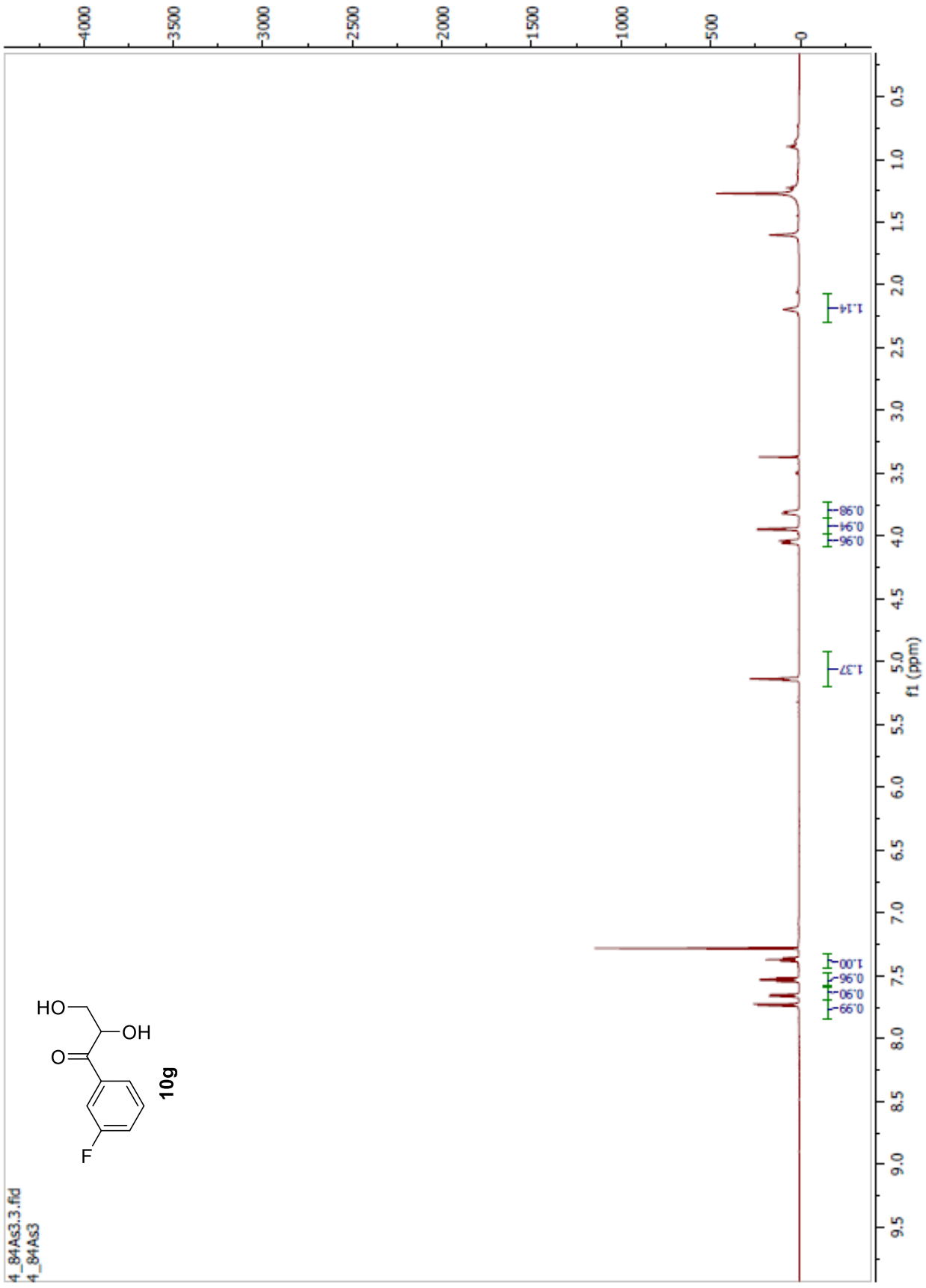

HO
OH
O
Br
10j
63.86
74.73
127.16
130.58
131.62
134.48
200.69
f1 (ppm)

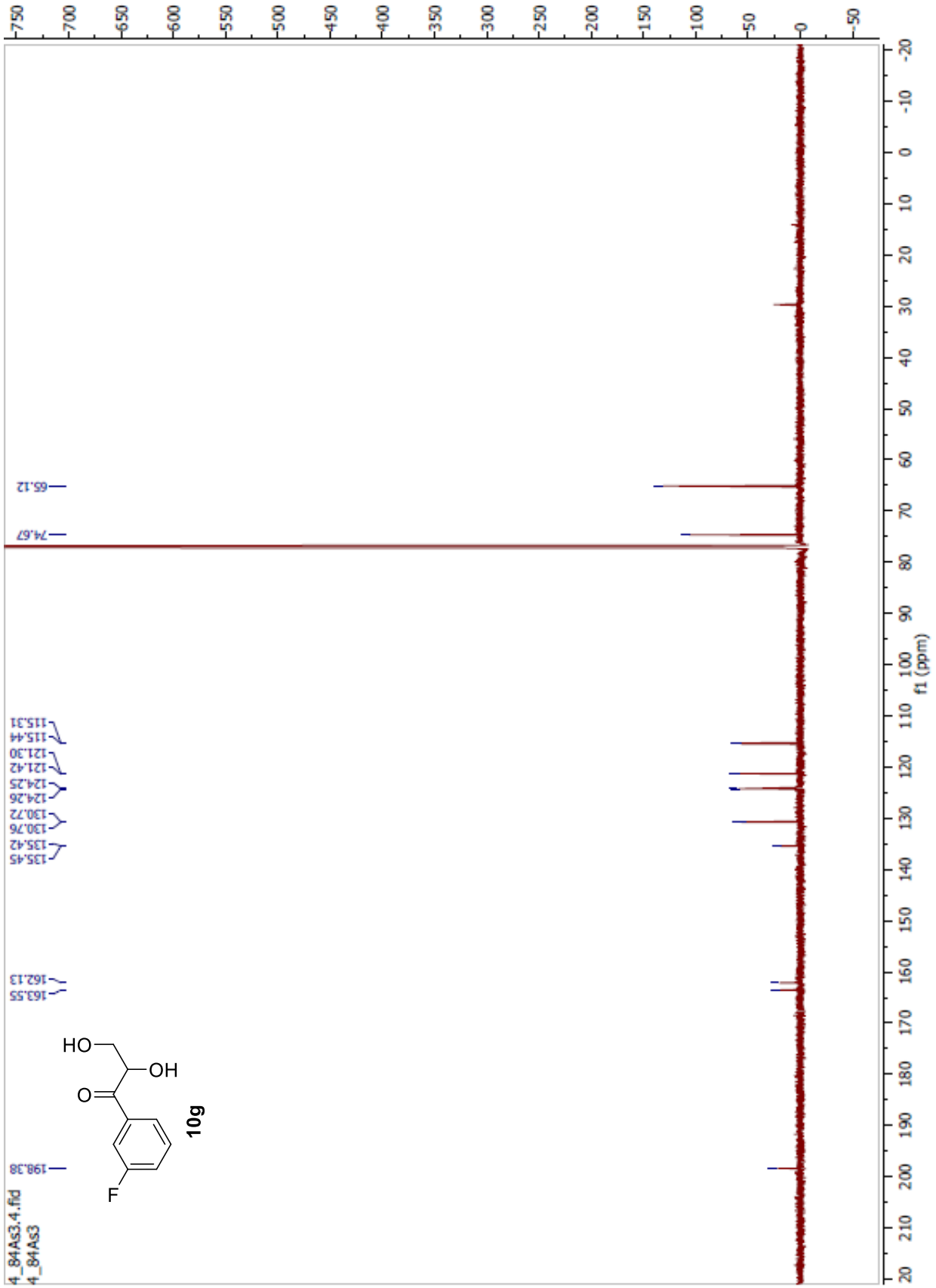

4_85Bs2.6.fid
4_85Bs2
HO
OH
O
O
10x
2.58
2.99
0.87
0.92
1.00
1.14
1.98
1.50
f1 (ppm)

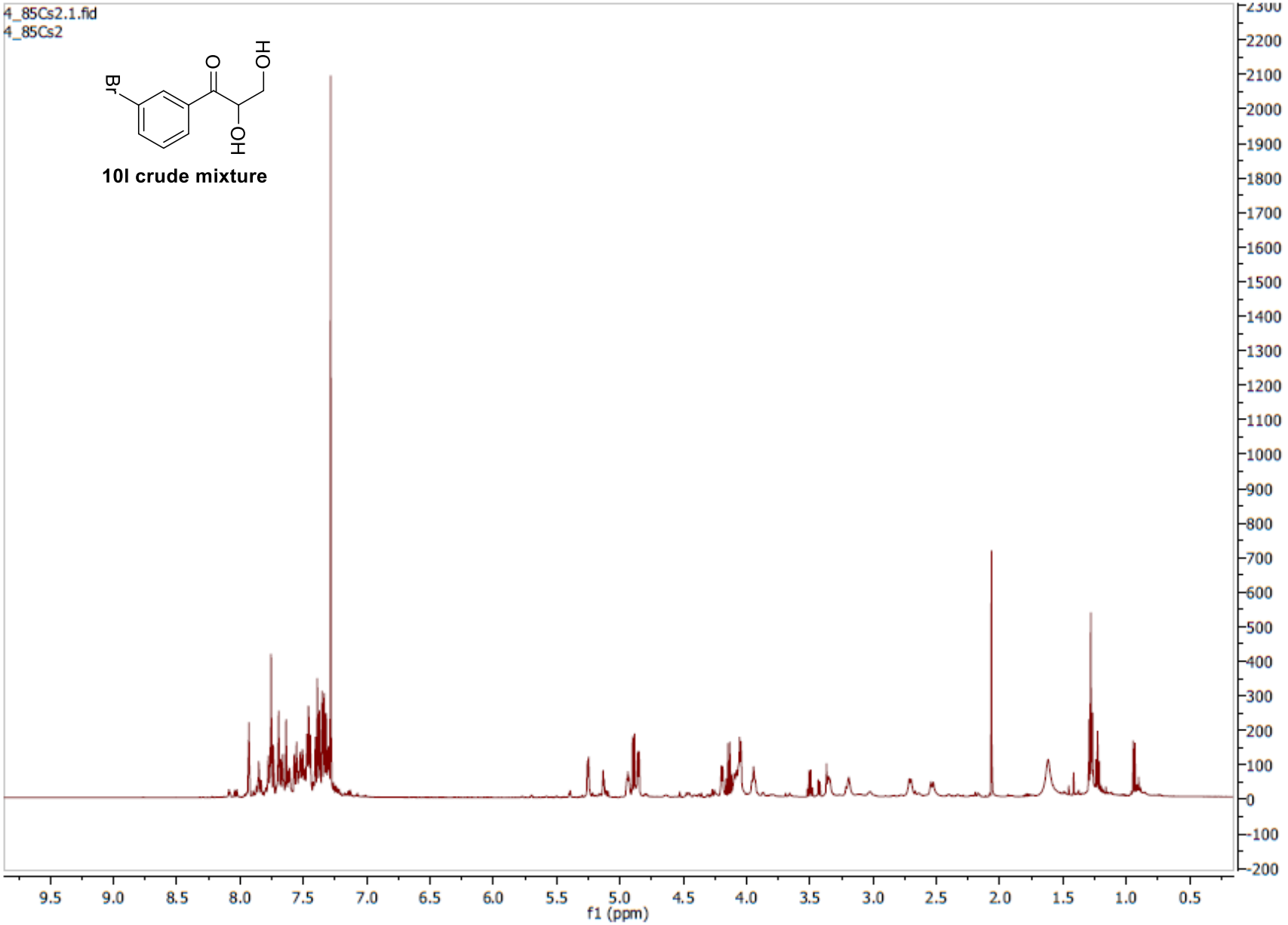

HO
OH
O
O
10x
159.26
136.77
129.76
120.89
119.04
113.07
74.51
64.03
55.31
f1 (ppm)

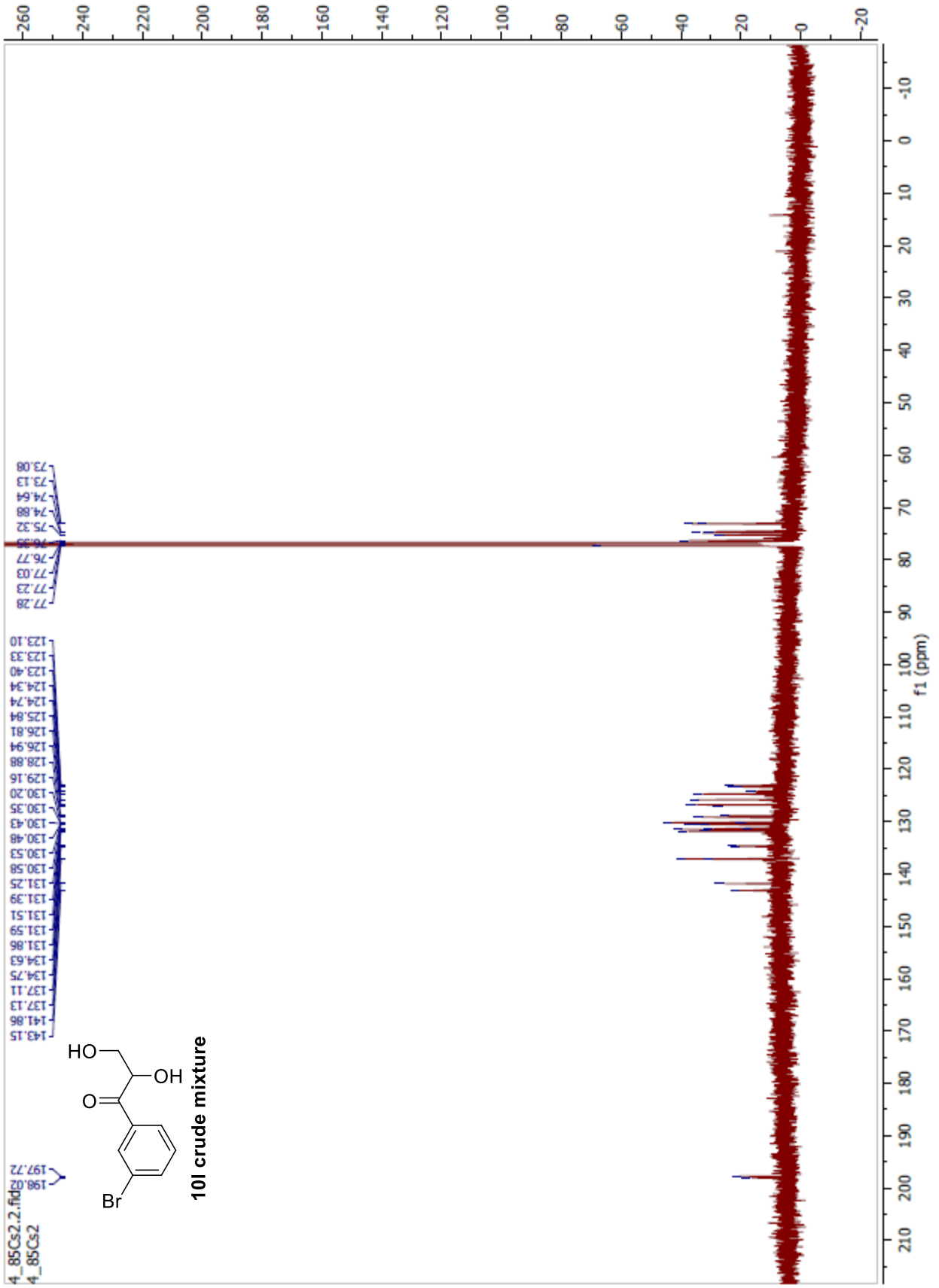

HO
OH
O
10y
1:3
HO
O
HO
17y
f1 (ppm)
4_86Cs2.1.fid
4_86Cs2

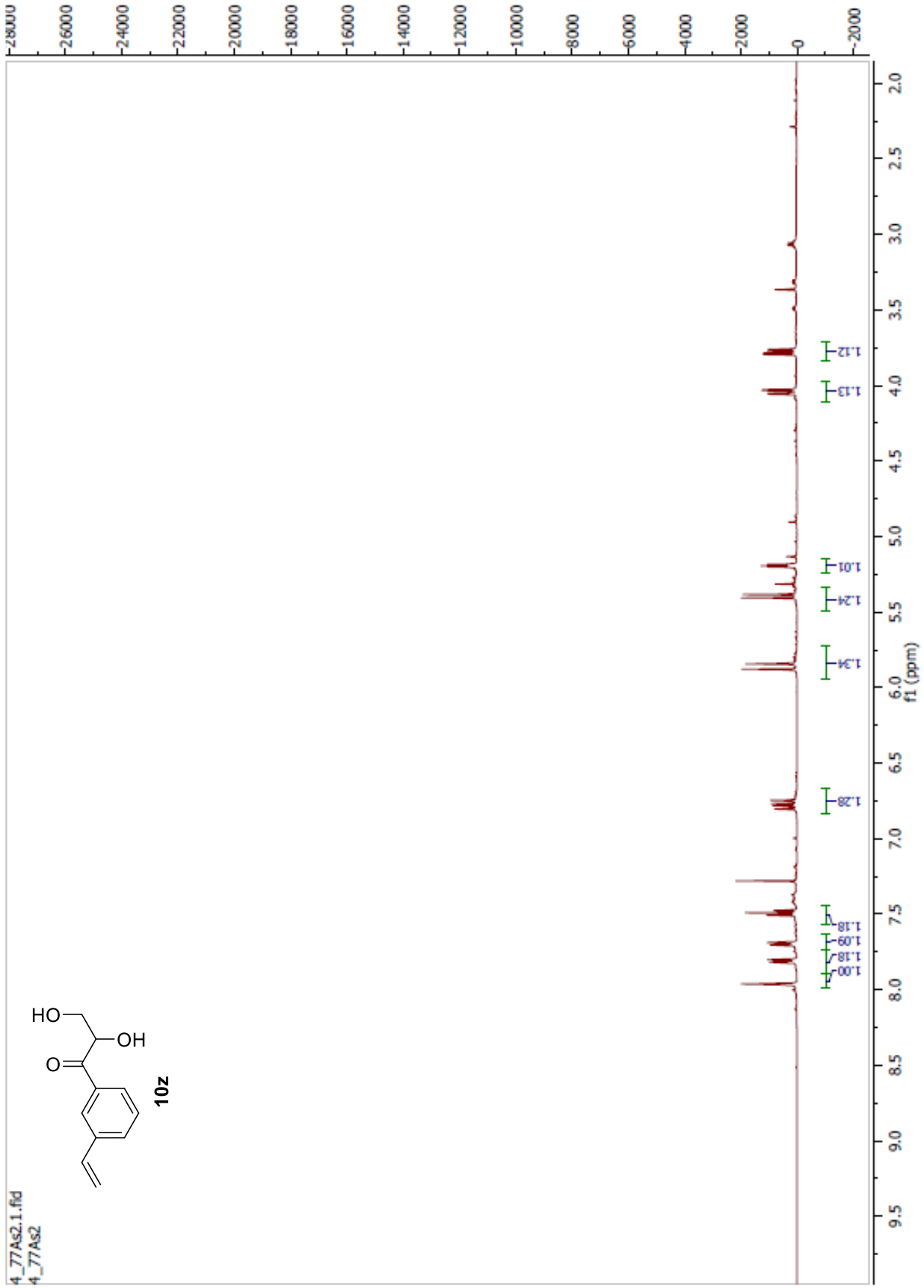

HO
OH
O
10y
1:3
HO
O
HO
17y
f1 (ppm)

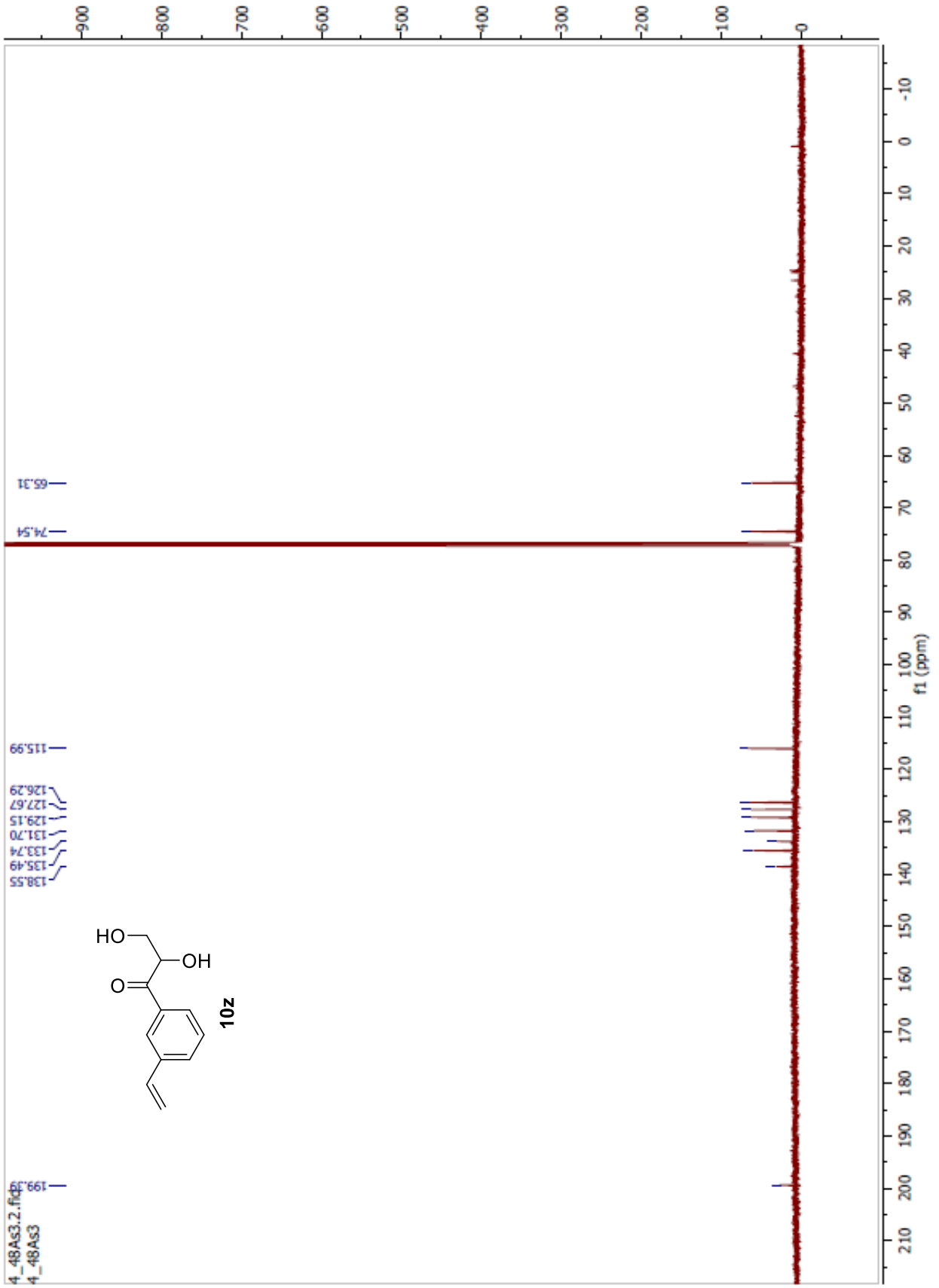

HO
OH
O
F
10g
4_84As3.3.fid
4_84As3
f1 (ppm)

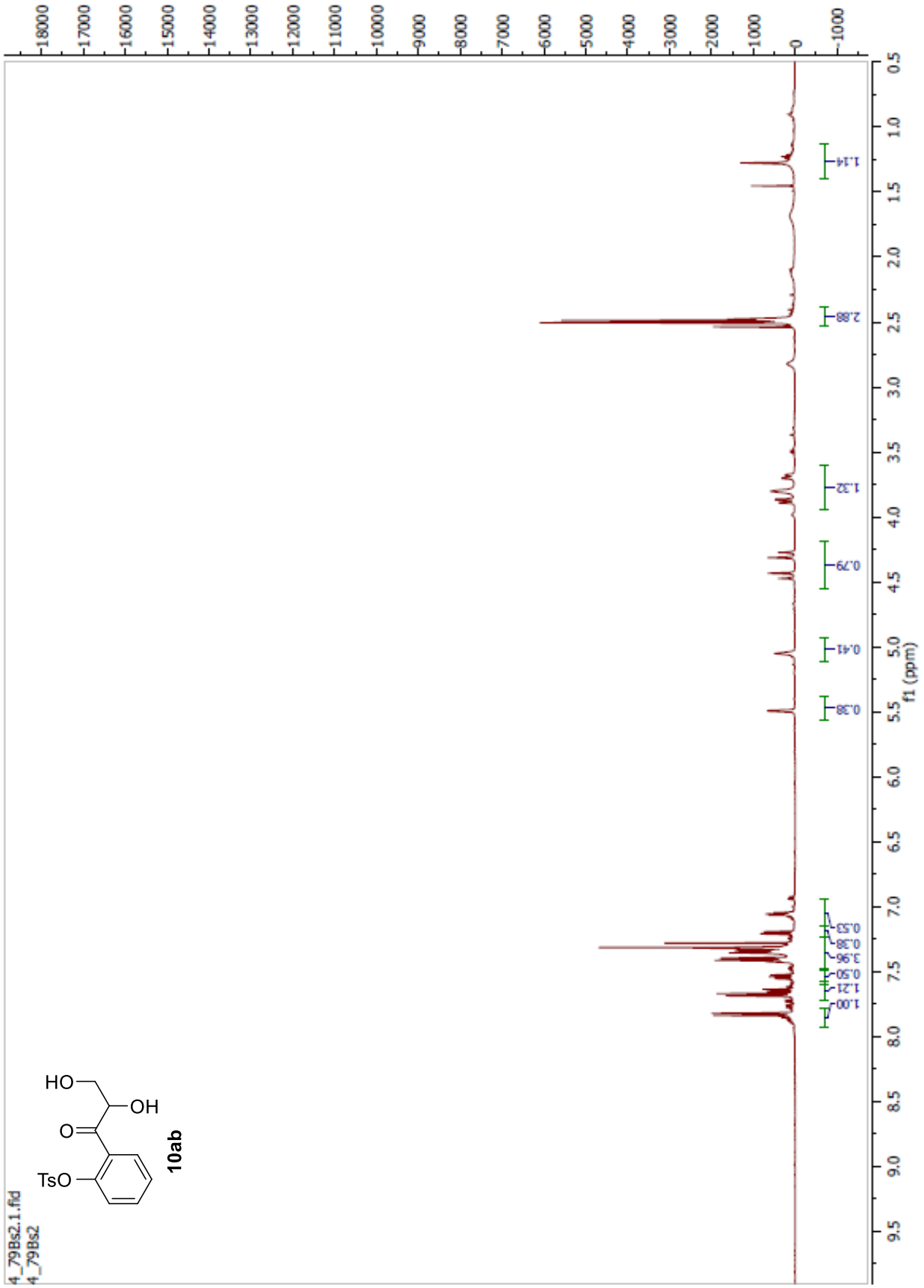

198.38
163.55
162.13
135.45
135.42
130.76
130.72
124.26
124.25
121.42
121.30
115.44
115.31
74.67
65.12
HO
OH
O
F
10g
f1 (ppm)

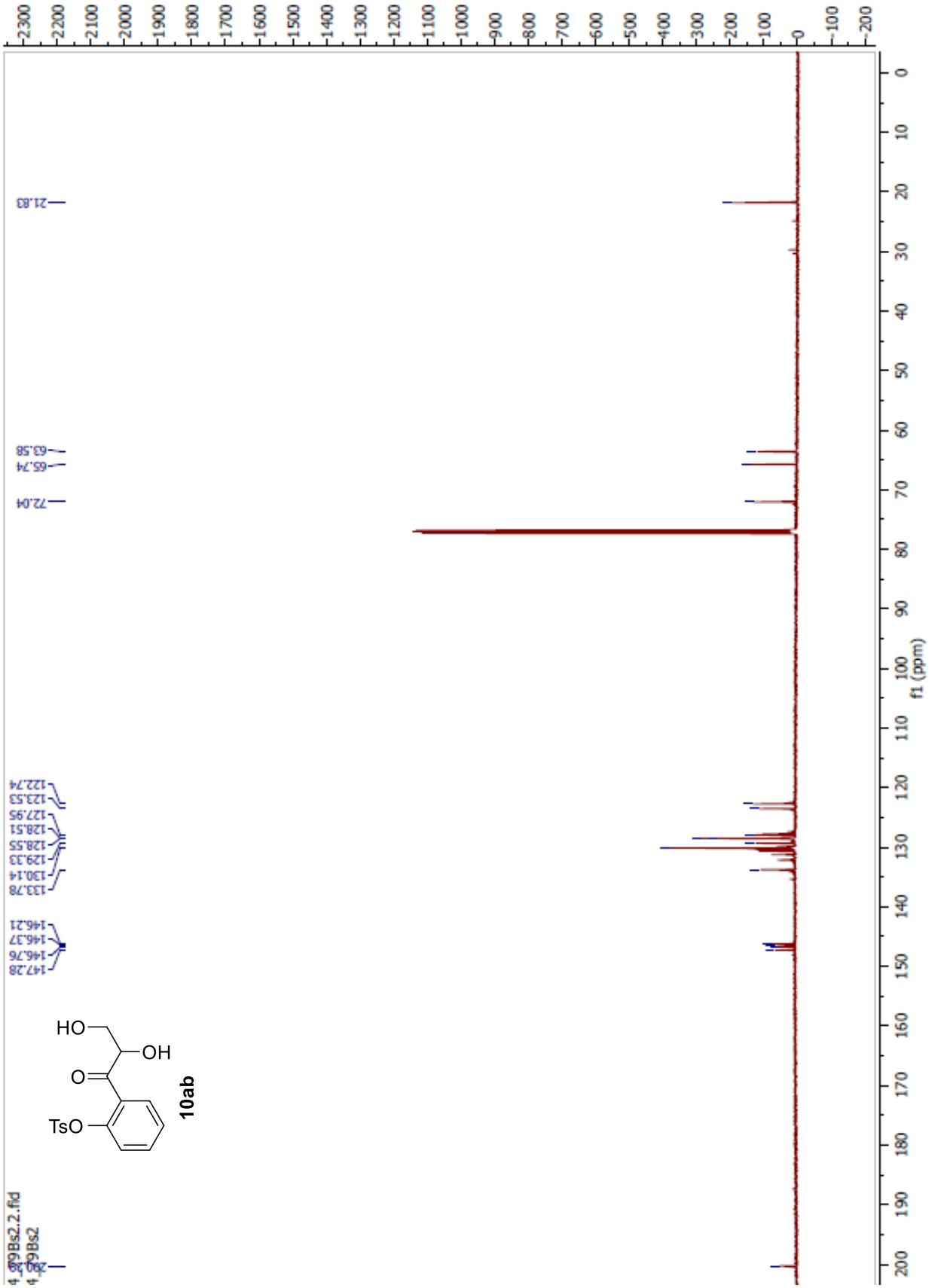

4_85Cs2.1.fid
4_85Cs2
Br
O
HO
OH
10l crude mixture
f1 (ppm)

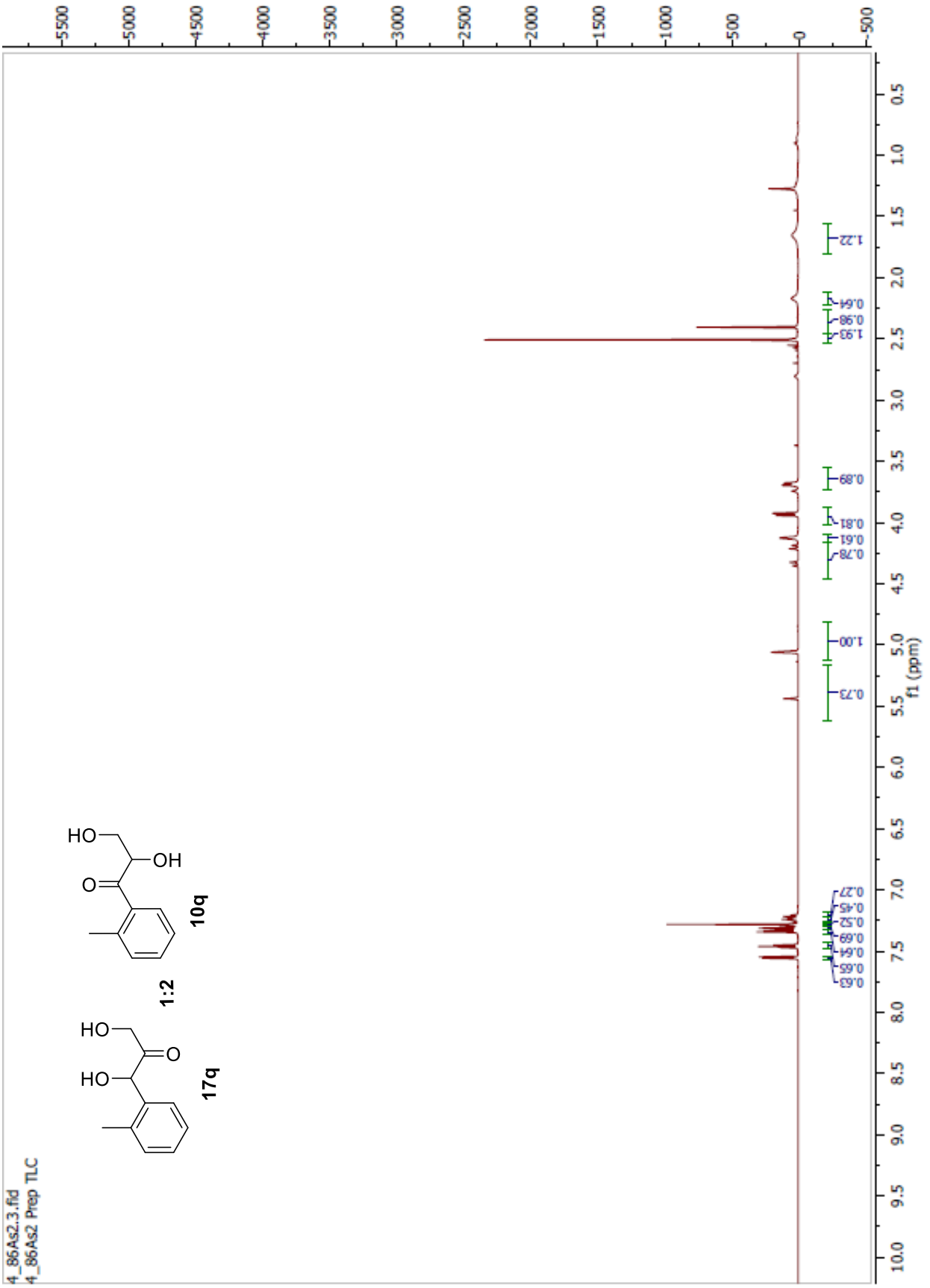

HO
OH
O
Br
10l crude mixture
f1 (ppm)

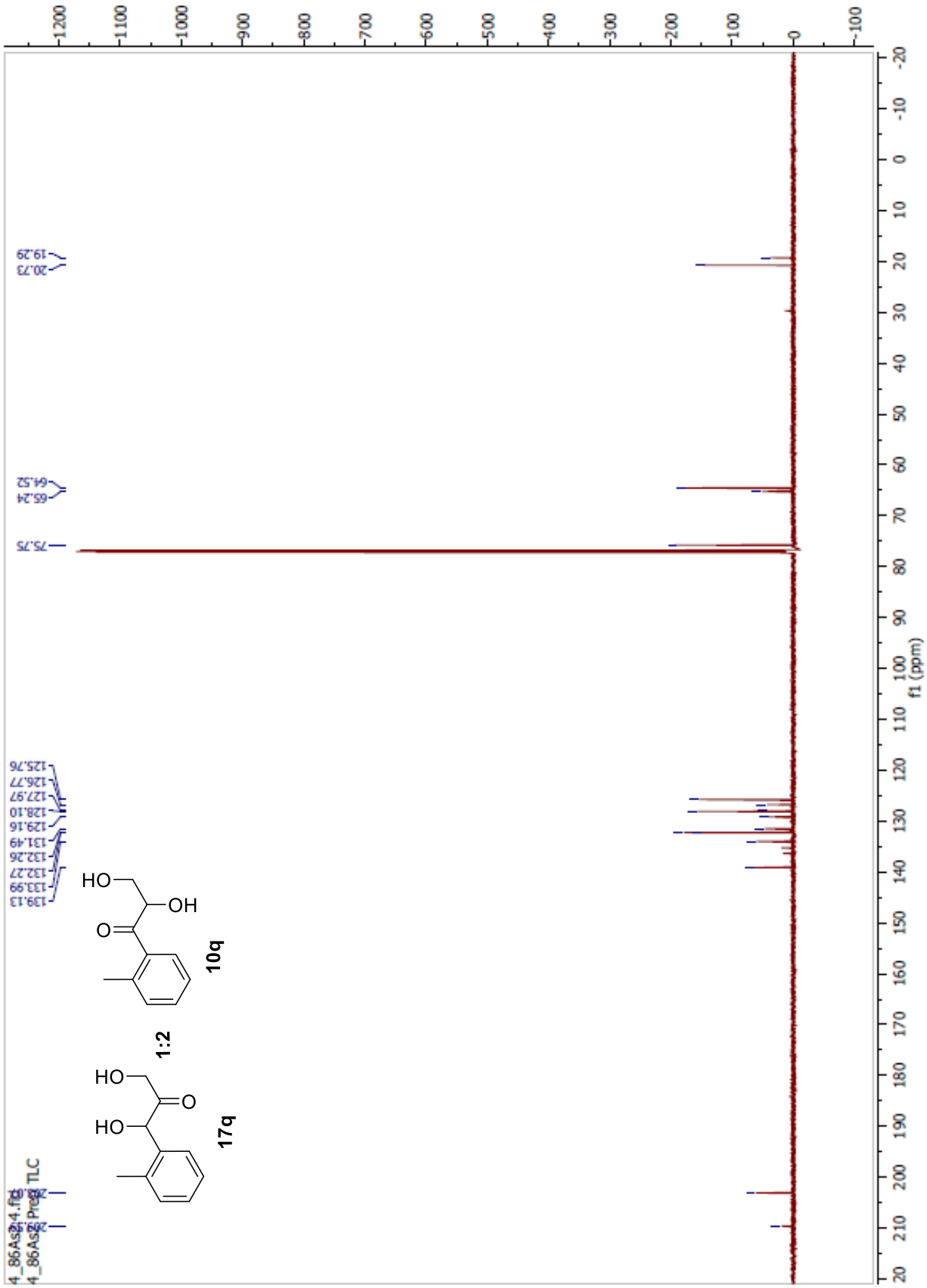

HO
OH
O
10z
4_77As2.1.fid
4_77As2
f1 (ppm)

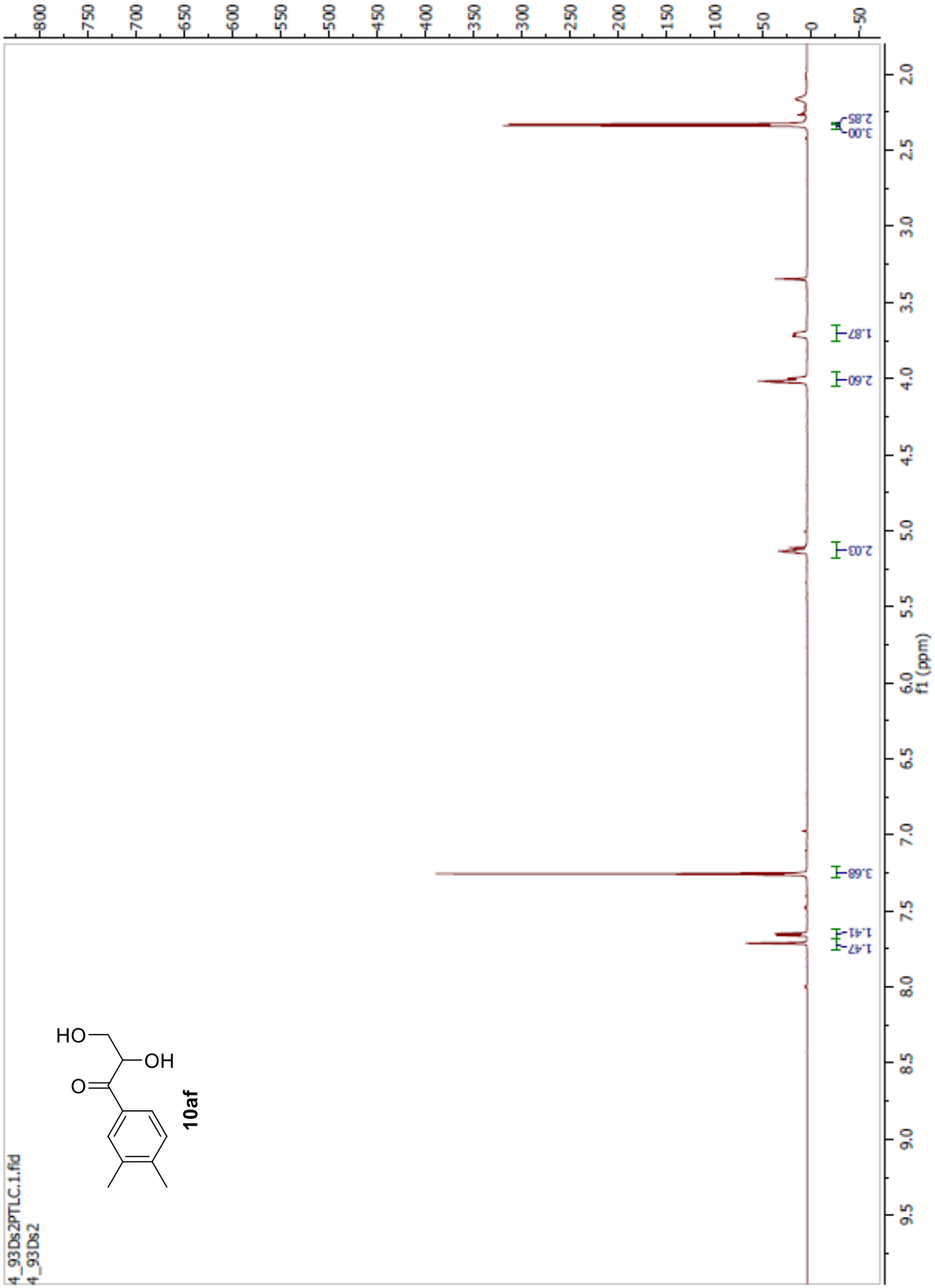

HO
OH
O
10z
65.31
74.54
115.99
126.29
127.67
129.15
131.70
133.74
135.49
138.55
199.39
4_48As3.2.fid
4_48As3
f1 (ppm)

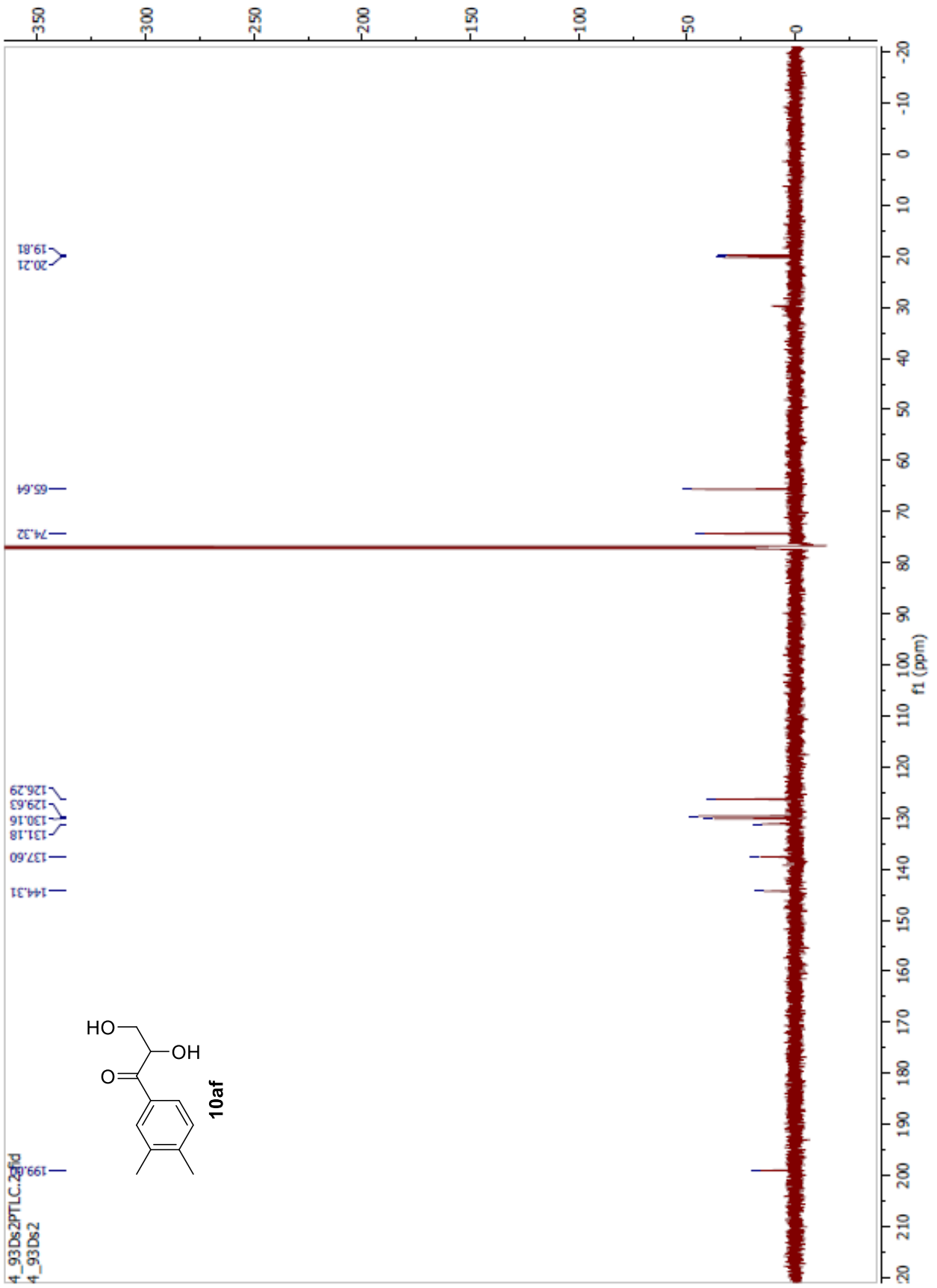

HO
OH
O
TsO
10ab
4_79Bs2.1.fid
4_79Bs2
f1 (ppm)

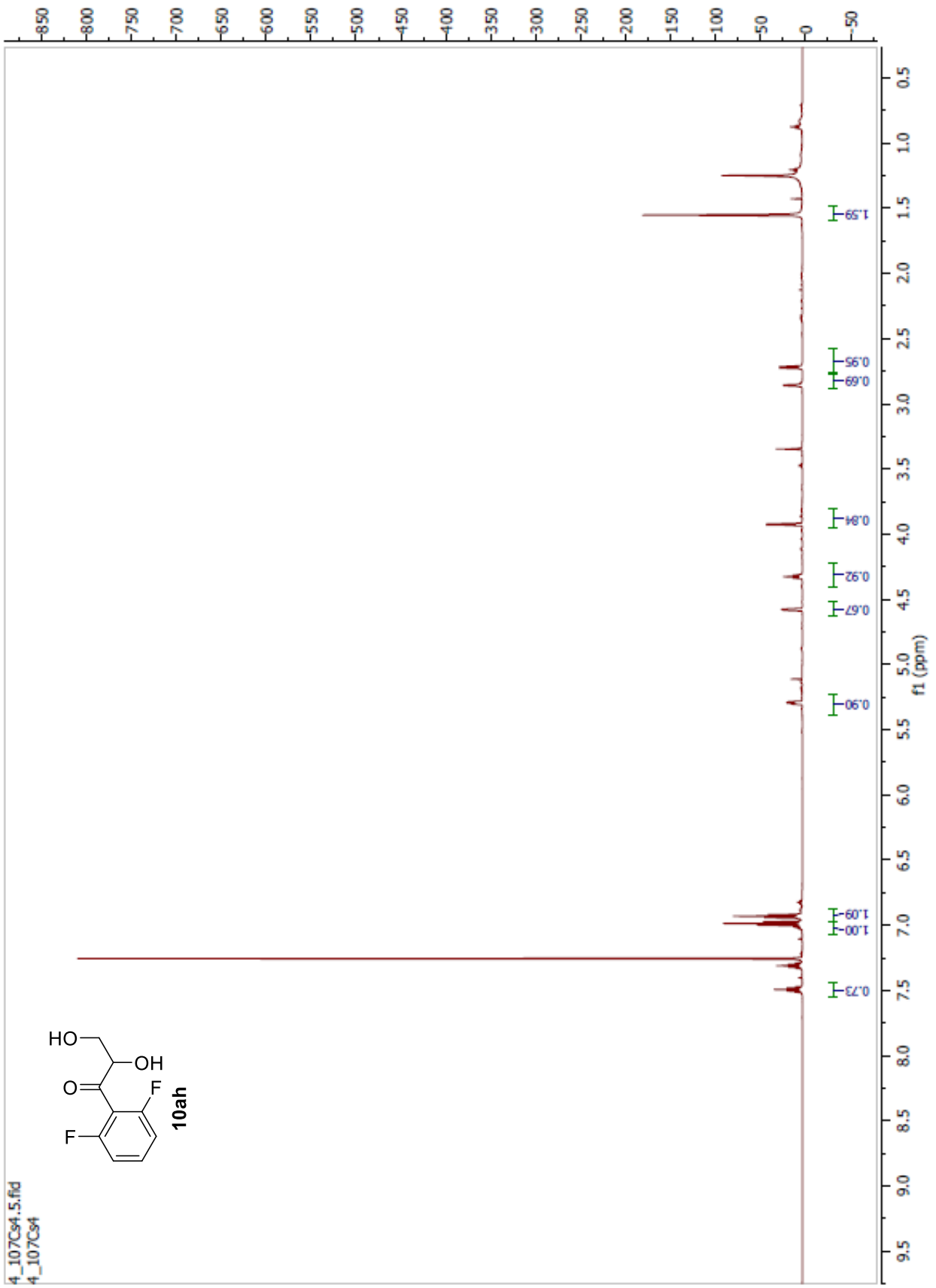

21.83
63.58
65.74
72.04
122.74
123.53
127.95
128.51
128.55
129.33
130.14
133.78
146.21
146.37
146.76
147.28
HO
OH
O
TsO
10ab
f1 (ppm)

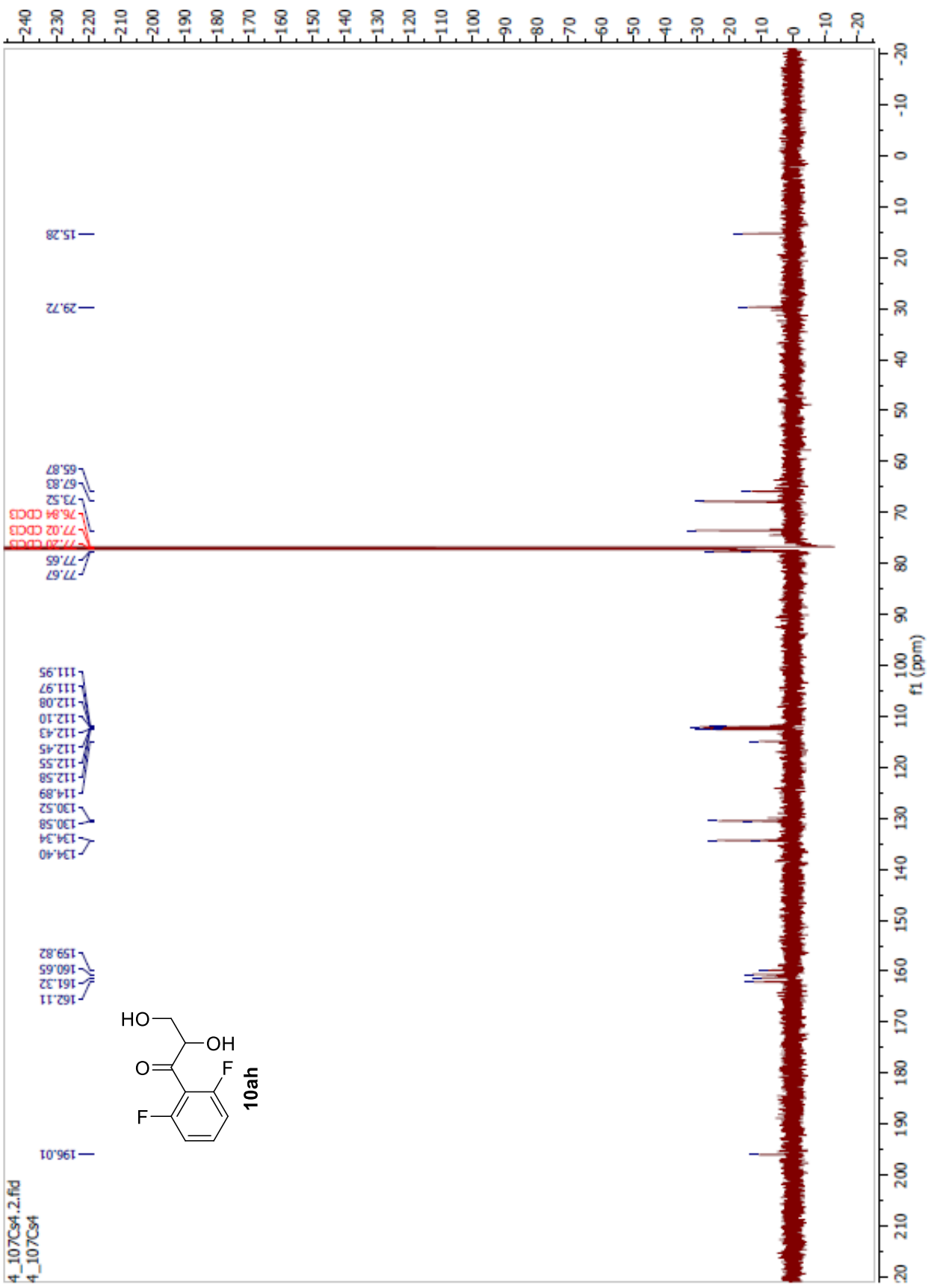

4_86As2.3.fid
4_86As2 Prep TLC
HO
OH
O
10q
1:2
HO
HO
O
17q
f1 (ppm)

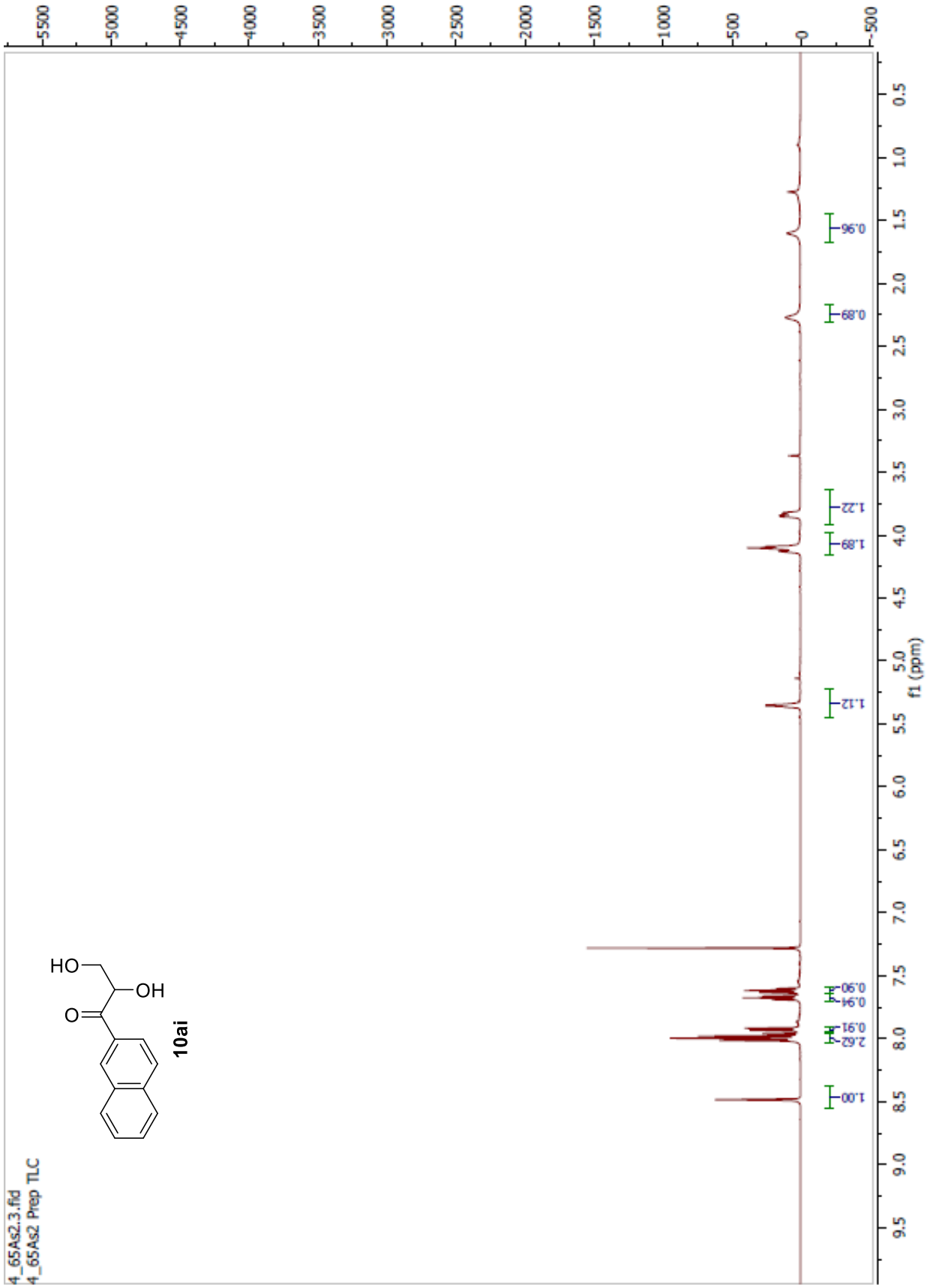

HO
OH
O
10q
1:2
HO
O
HO
17q
f1 (ppm)

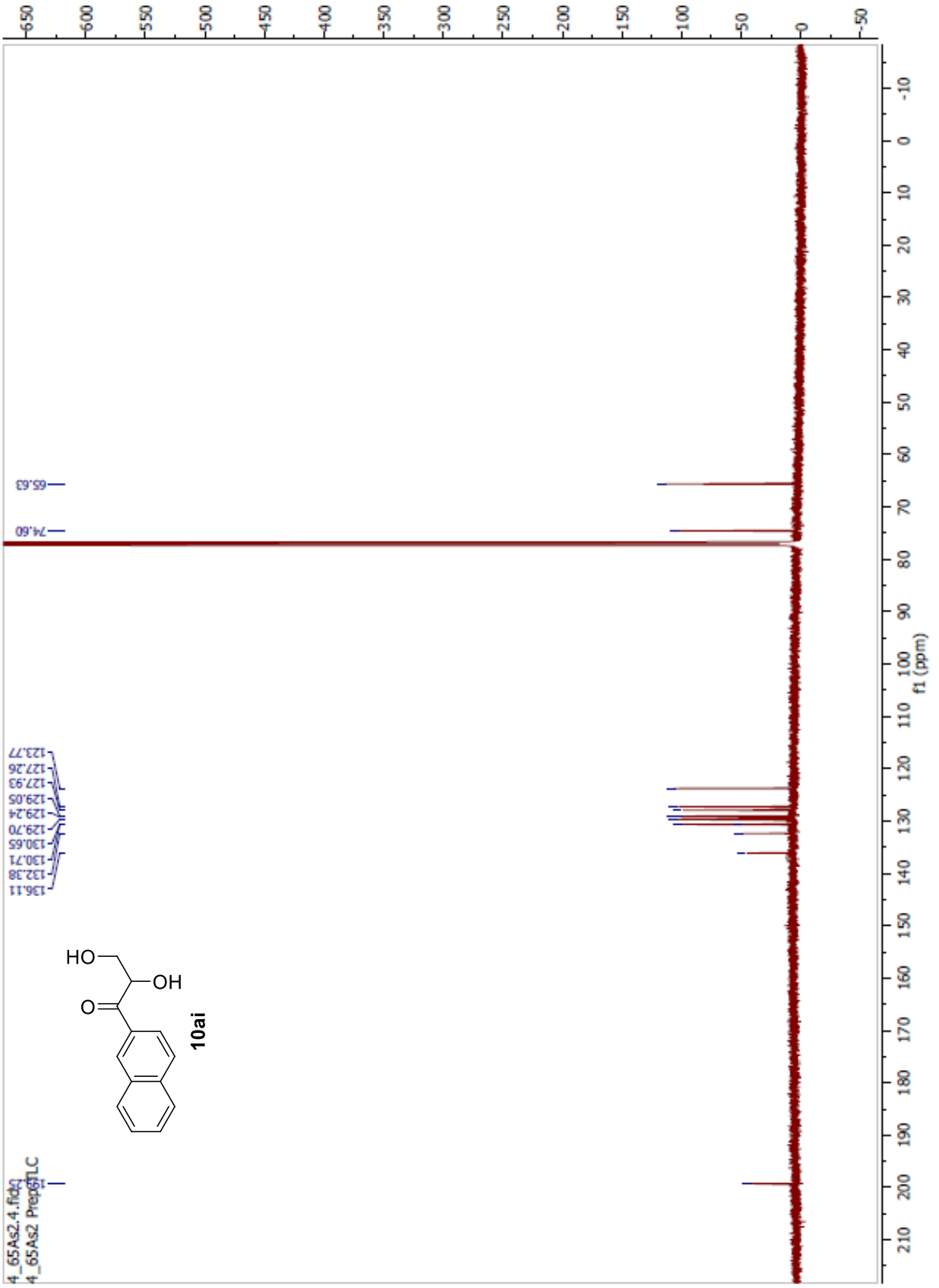

4_93Ds2PTLC.1.fid
4_93Ds2
HO
OH
O
10af
f1 (ppm)
3.00
2.85
1.87
2.60
2.03
3.69
1.47
1.41

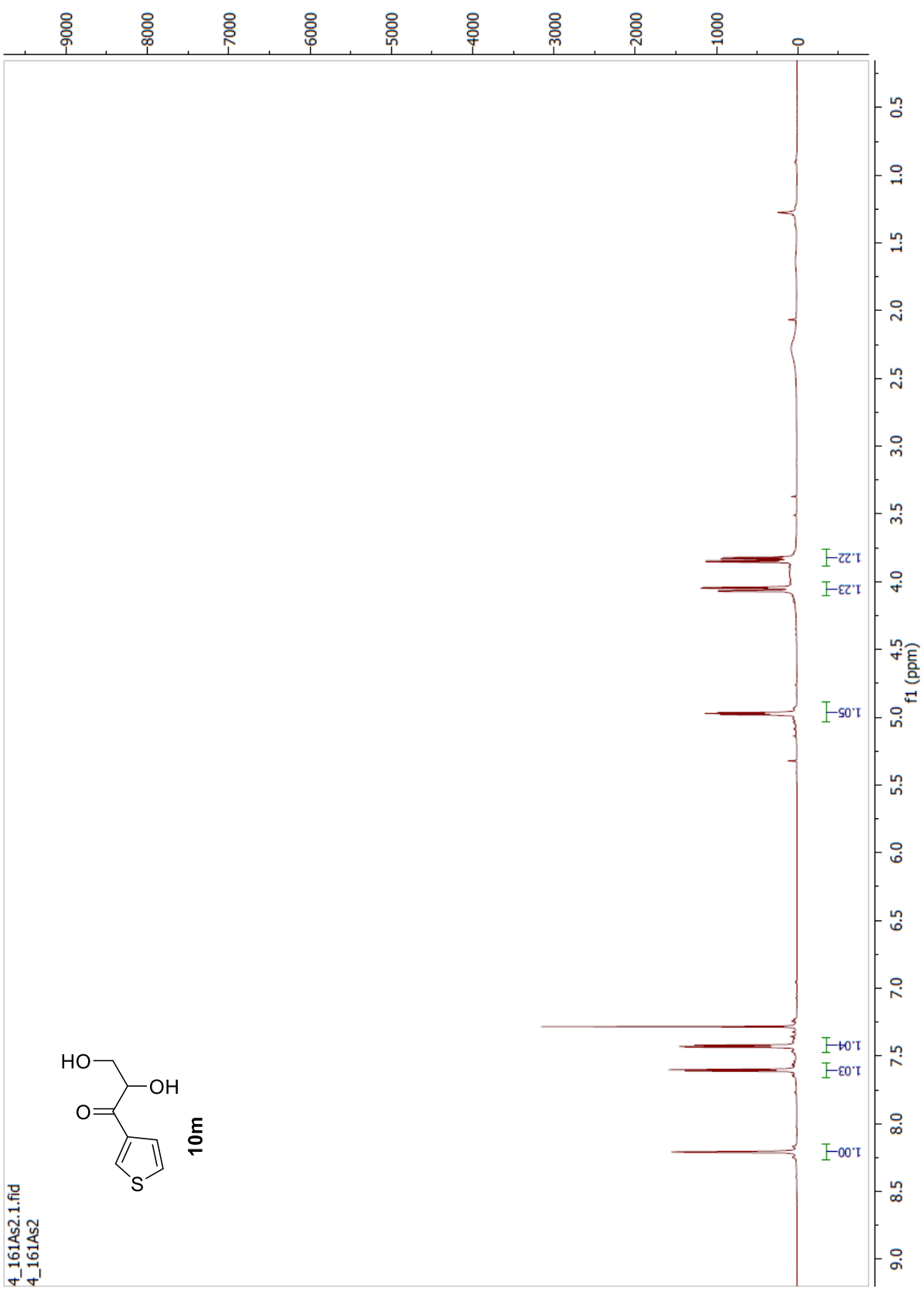

HO
OH
O
10af
199.66
144.31
137.60
131.18
130.16
129.63
126.29
74.32
65.64
20.21
19.81
f1 (ppm)

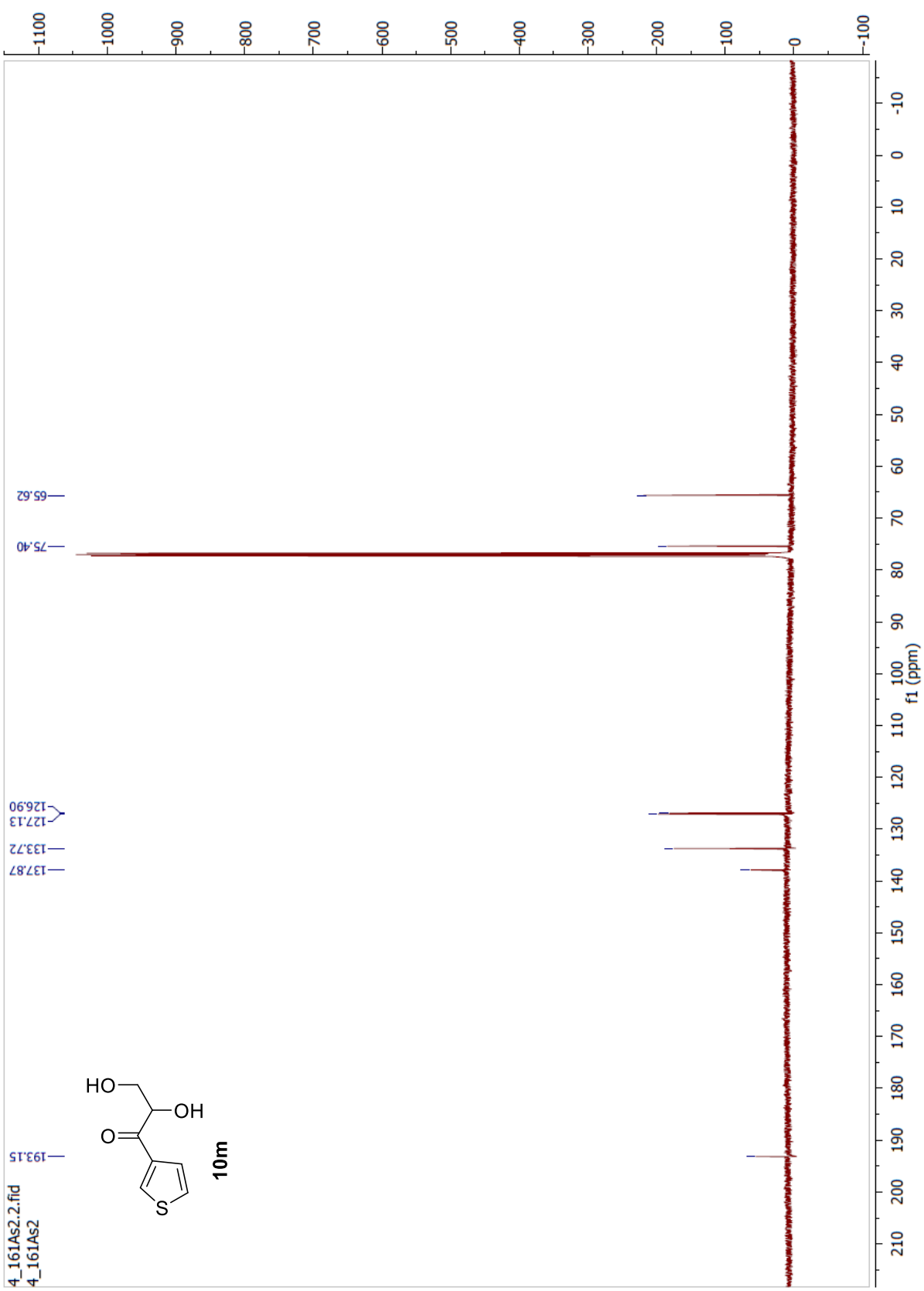

HO
OH
O
F
F
10ah
4_107Cs4.5.fid
4_107Cs4
f1 (ppm)

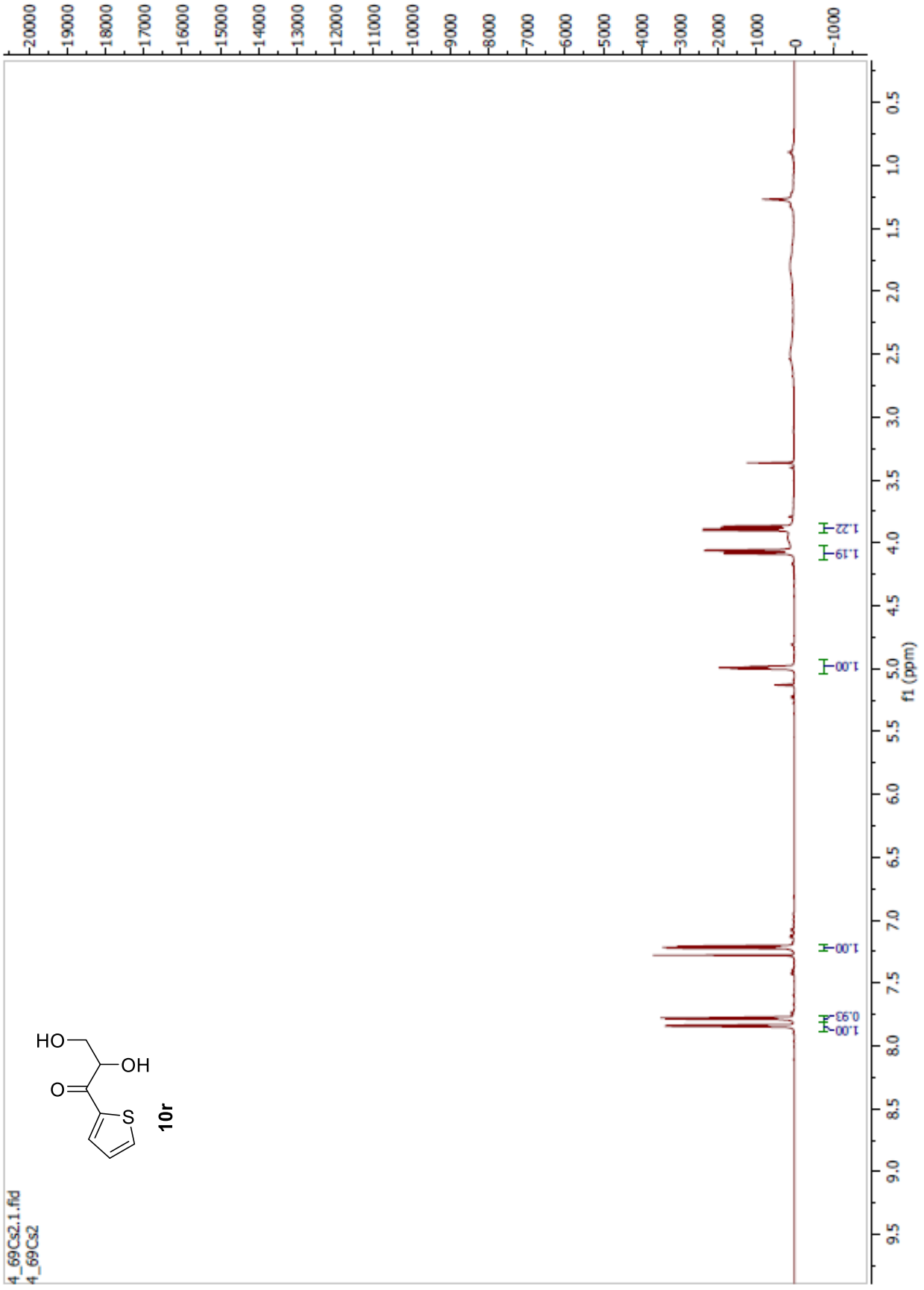

HO
OH
O
F
F
10ah
f1 (ppm)
4_107Cs4.2.fid
4_107Cs4

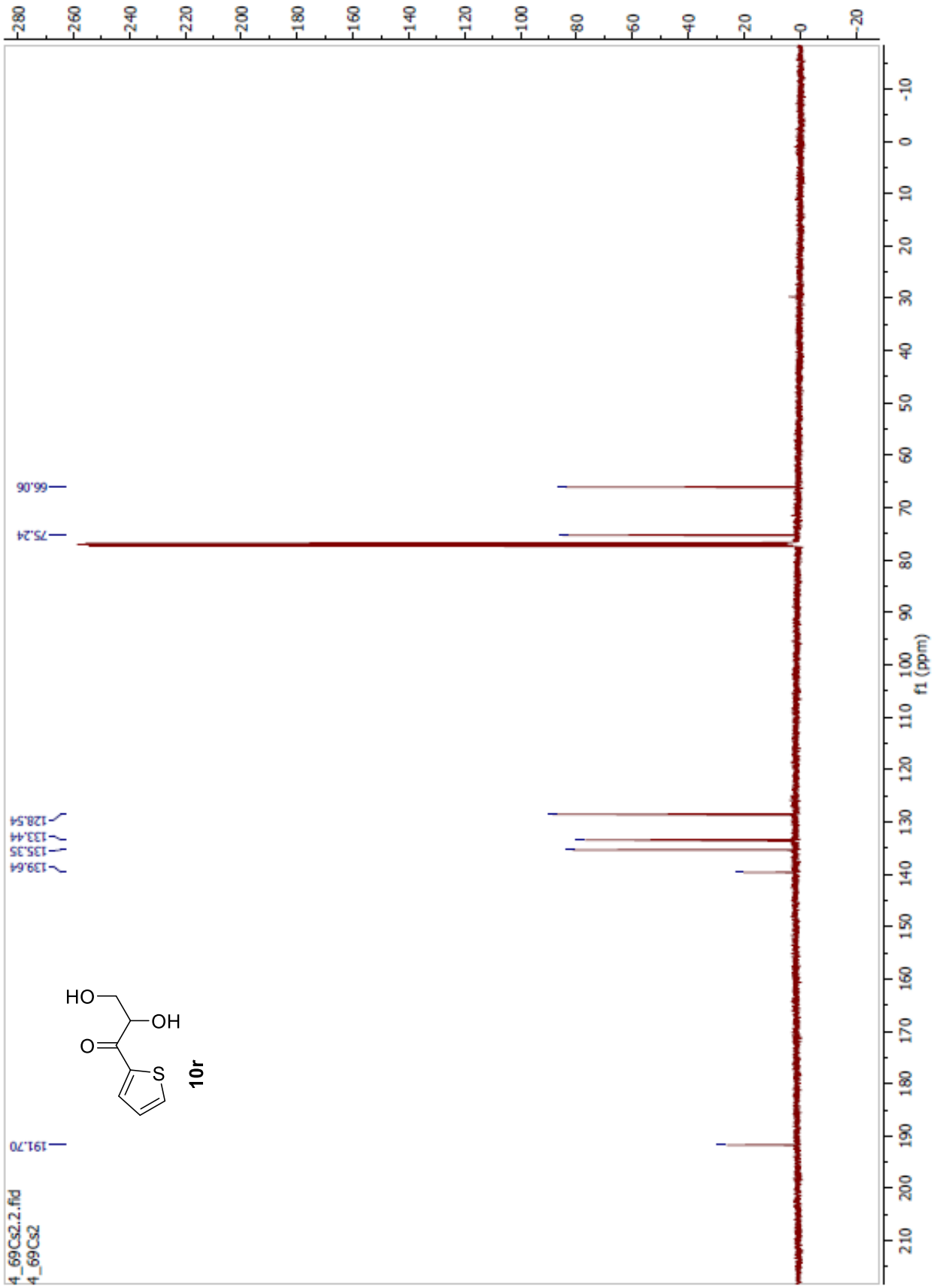

HO
OH
O
10ai
4_65As2.3.fid
4_65As2 Prep TLC
f1 (ppm)
0.96
0.89
1.22
1.89
1.12
0.90
0.94
0.91
2.62
1.00

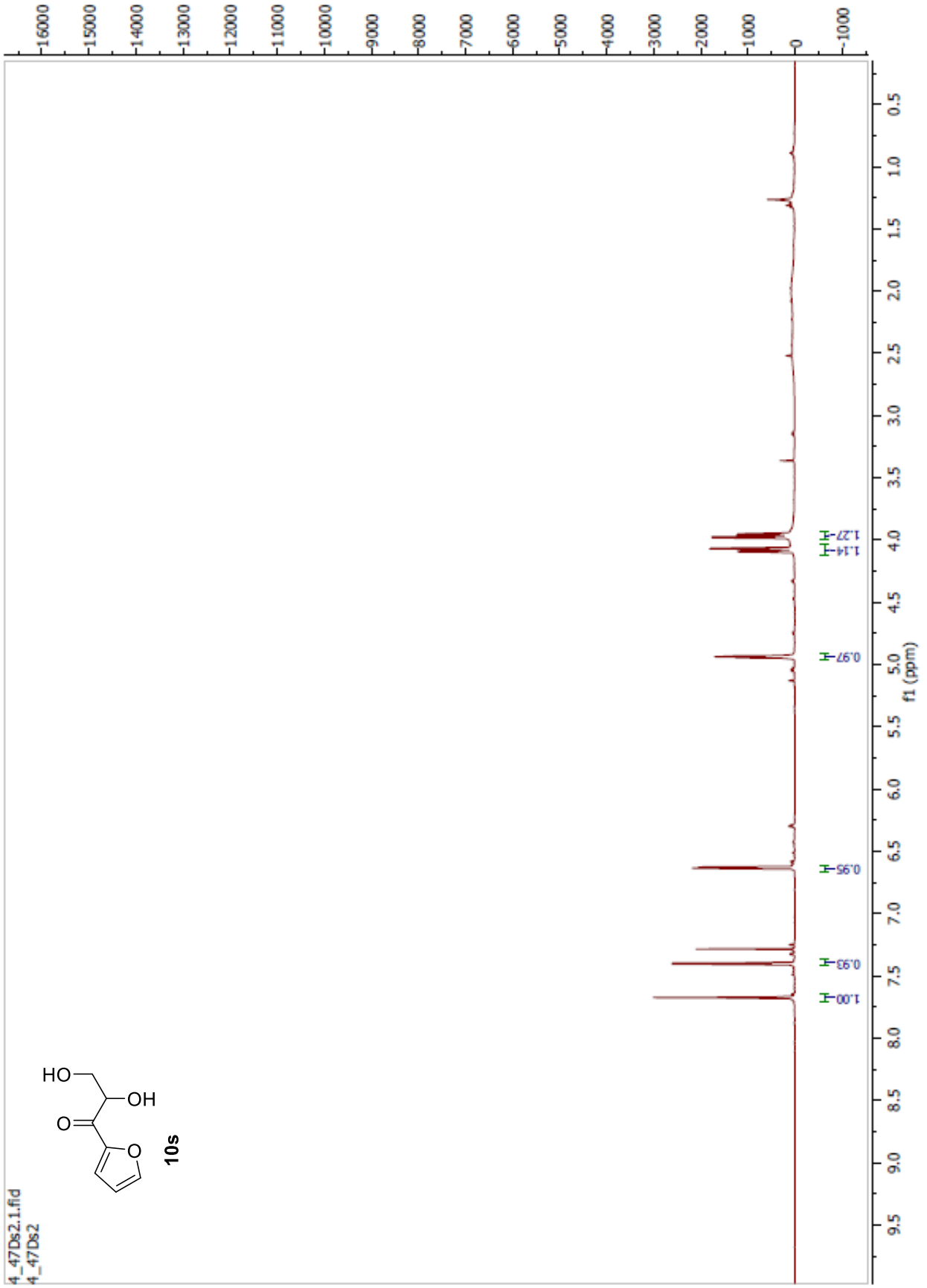

HO
OH
O
10ai
65.63
74.60
123.77
127.26
127.93
129.05
129.24
129.70
130.65
130.71
132.38
136.11
f1 (ppm)

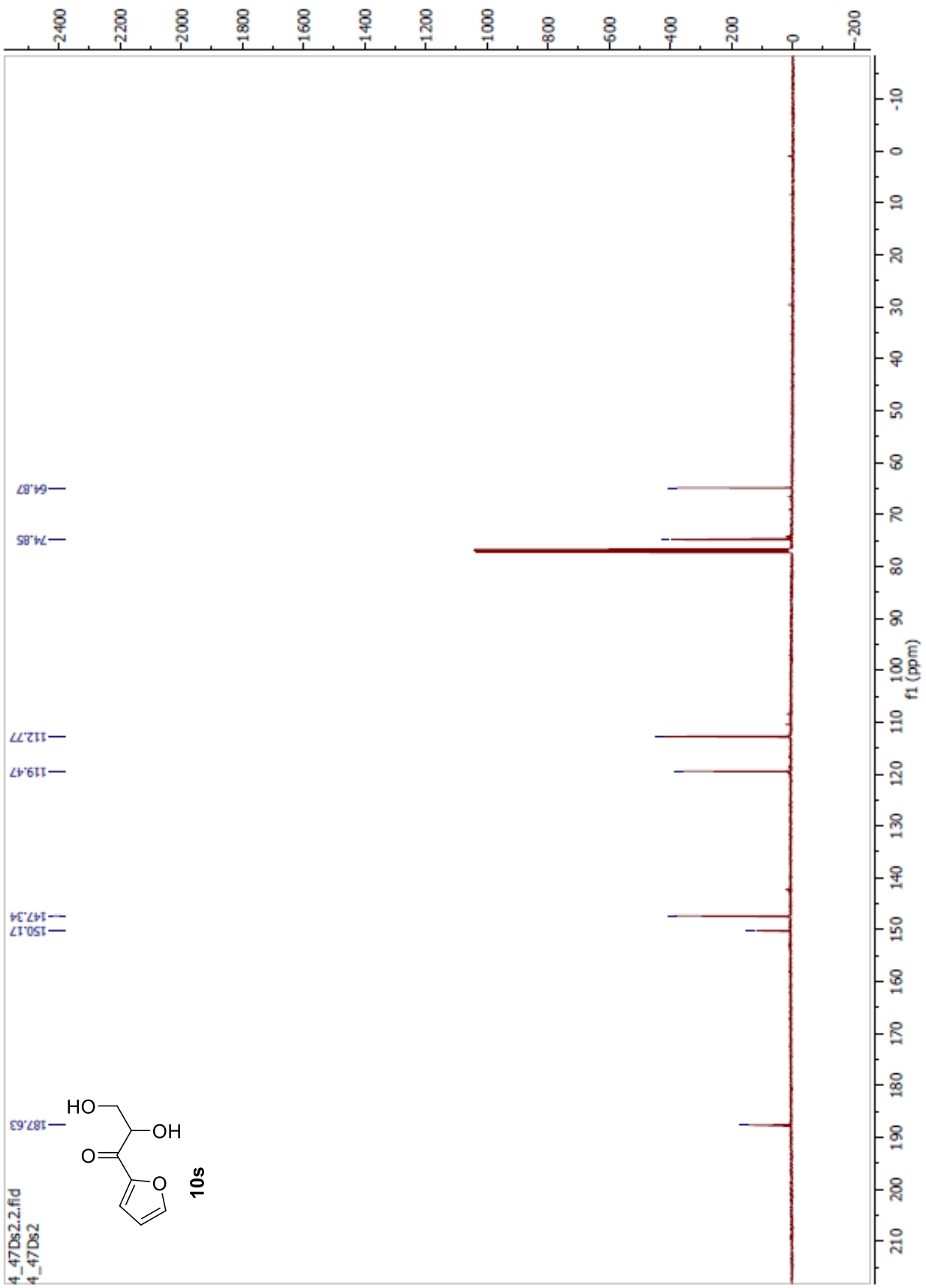

4_161As2.1.fid
4_161As2
HO
OH
O
S
10m
1.00
1.04
1.03
1.05
1.23
1.22
f1 (ppm)

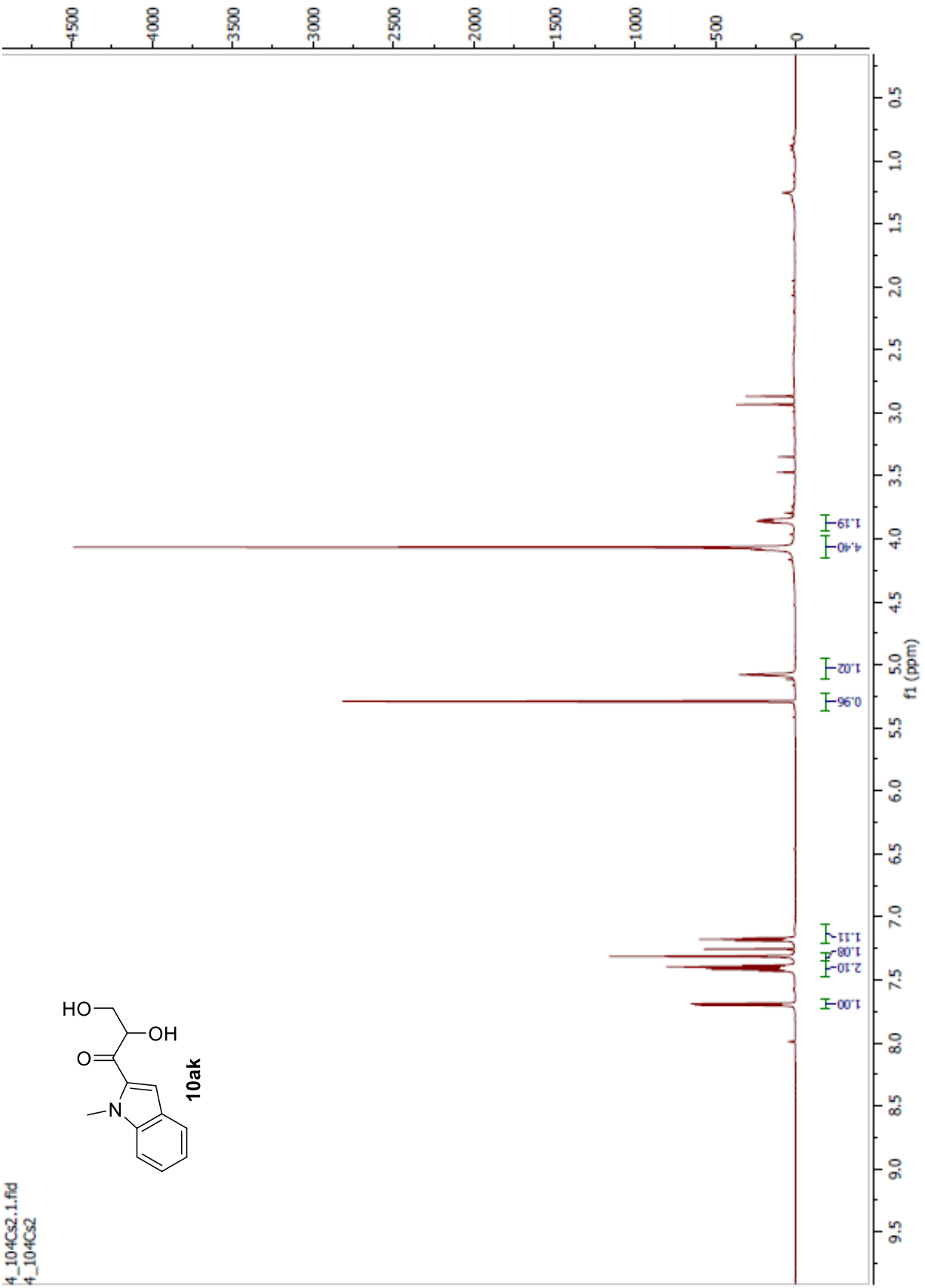

193.15
137.87
133.72
127.13
126.90
75.40
65.62
HO
OH
O
S
10m
4_161As2.2.fid
4_161As2
f1 (ppm)

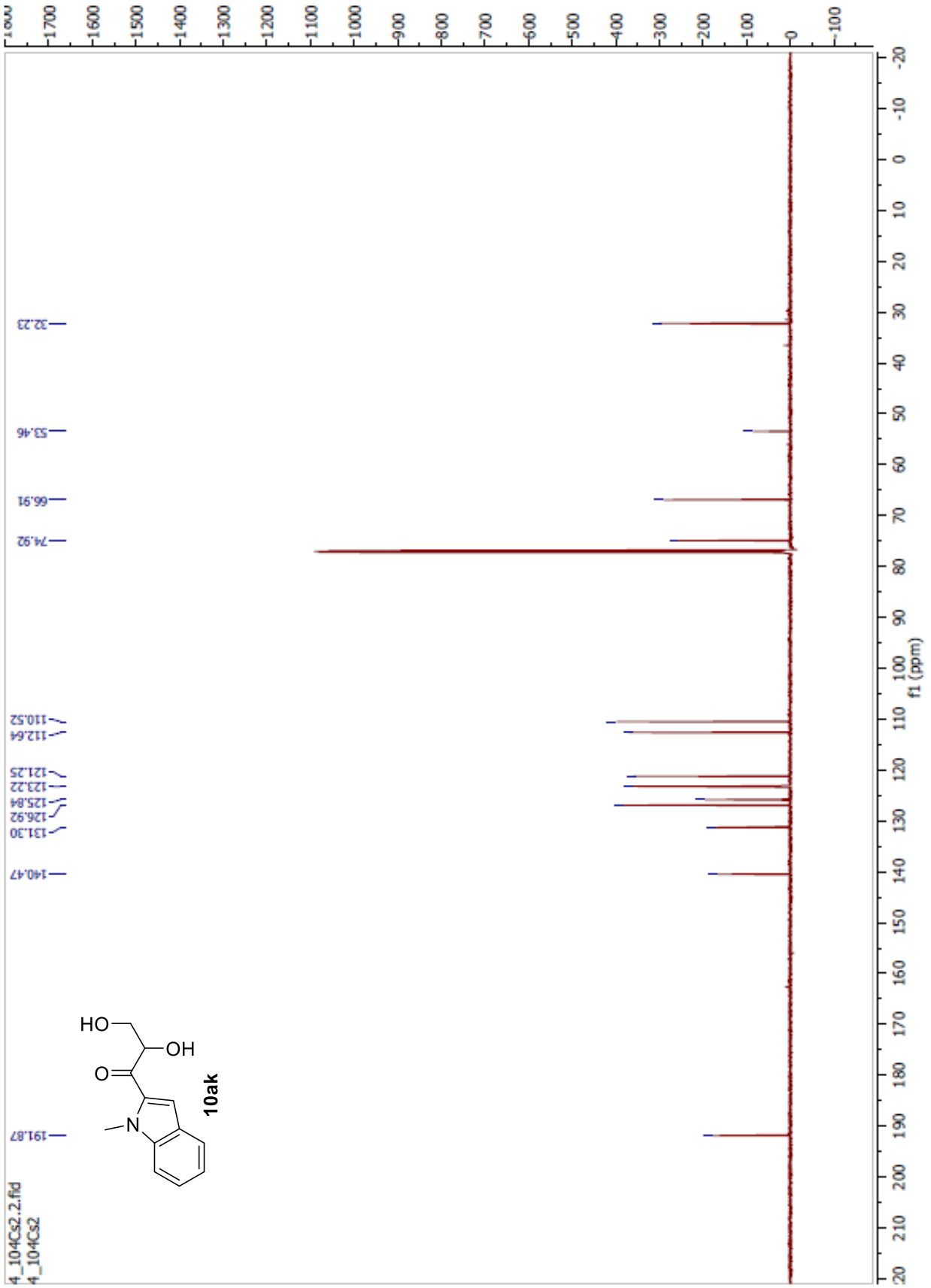

HO
OH
O
S
10r
4_69Cs2.1.fid
4_69Cs2
1.22
1.19
1.00
1.00
0.93
1.00
f1 (ppm)

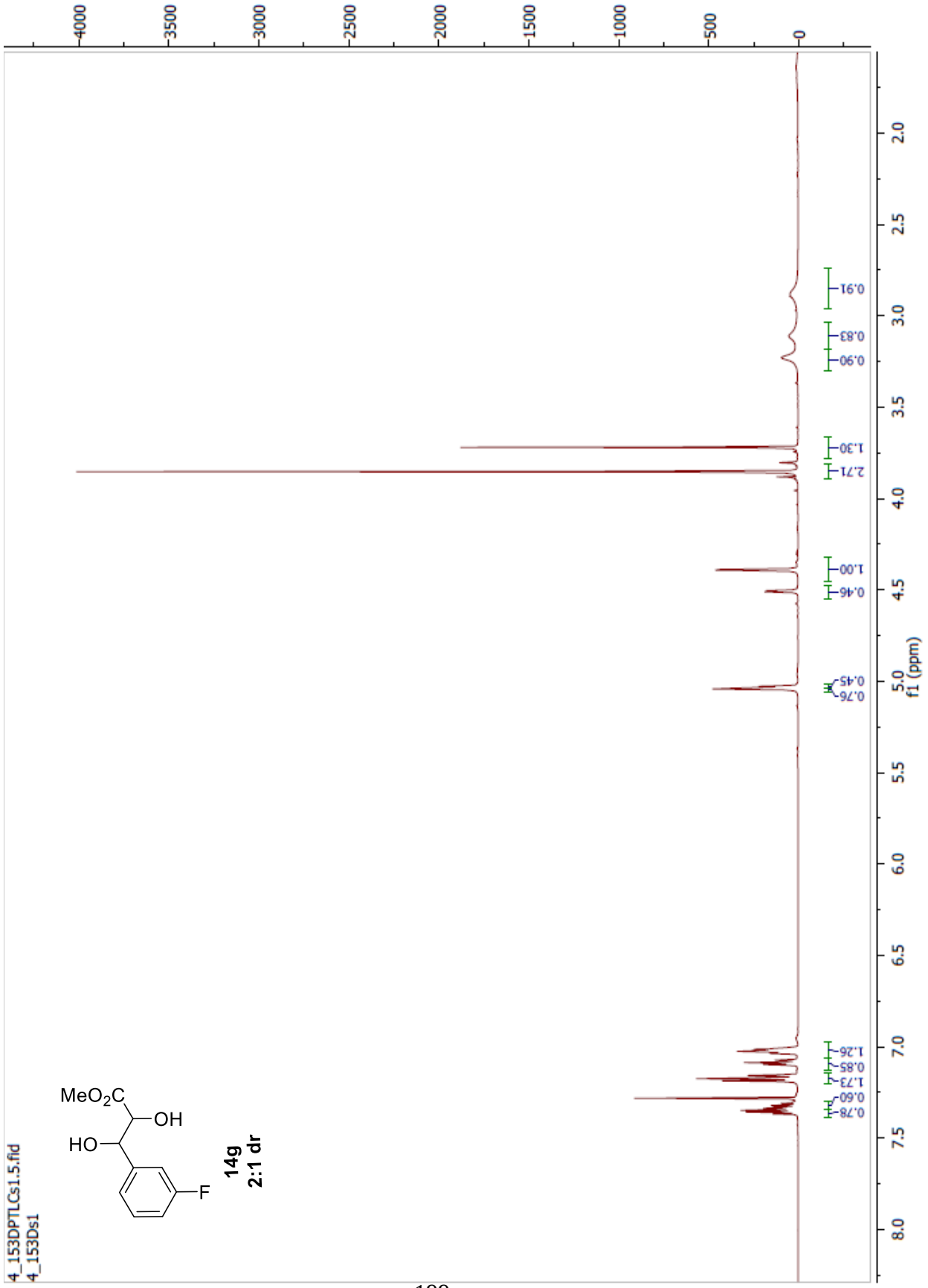

191.70
139.64
135.35
133.44
128.54
75.24
66.06
HO
OH
O
S
10r
4_69Cs2.2.fid
4_69Cs2
f1 (ppm)

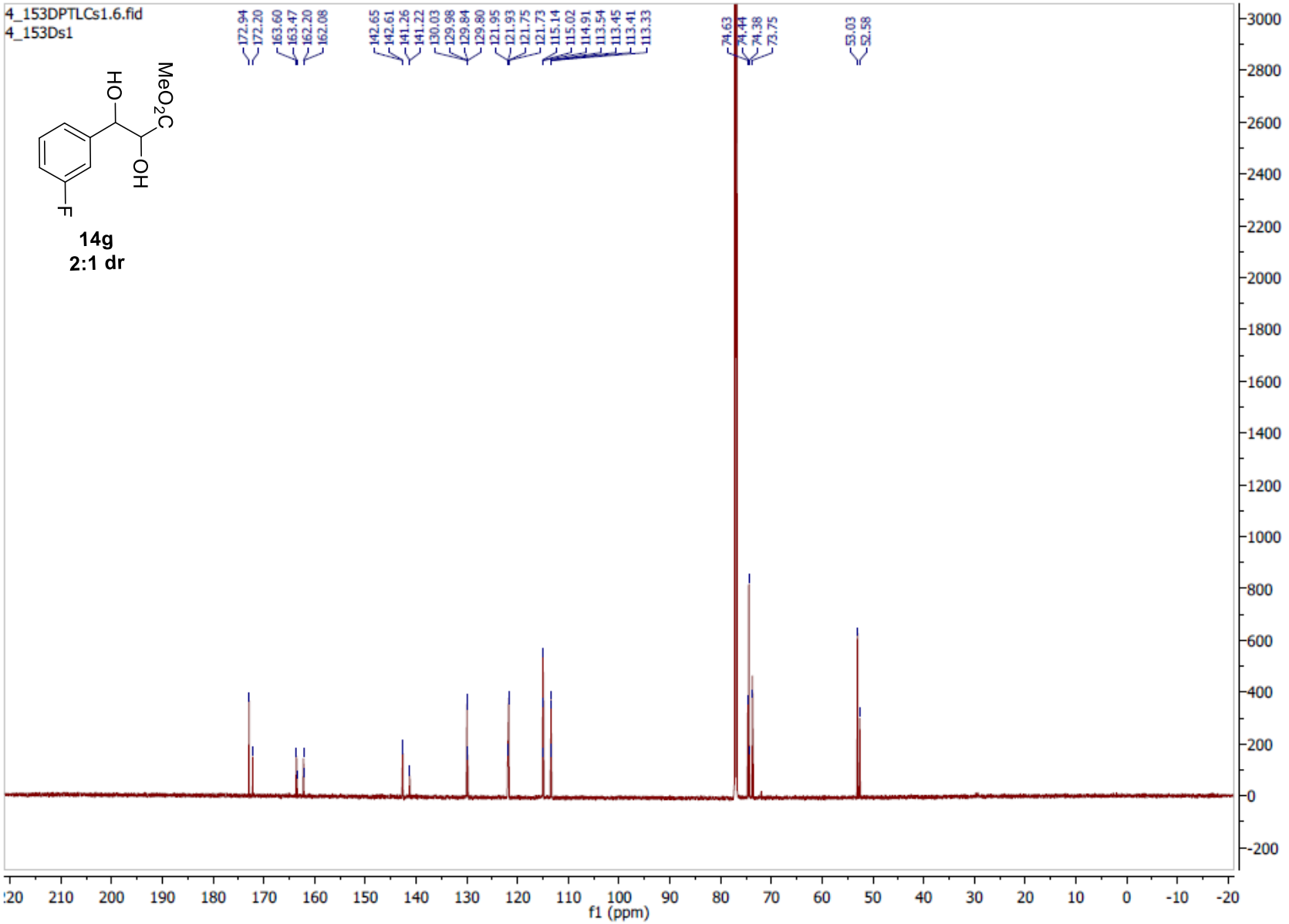

HO
OH
O
O
10s
4_47Ds2.1.fid
4_47Ds2
1.27
1.14
0.97
0.95
0.93
1.00
f1 (ppm)

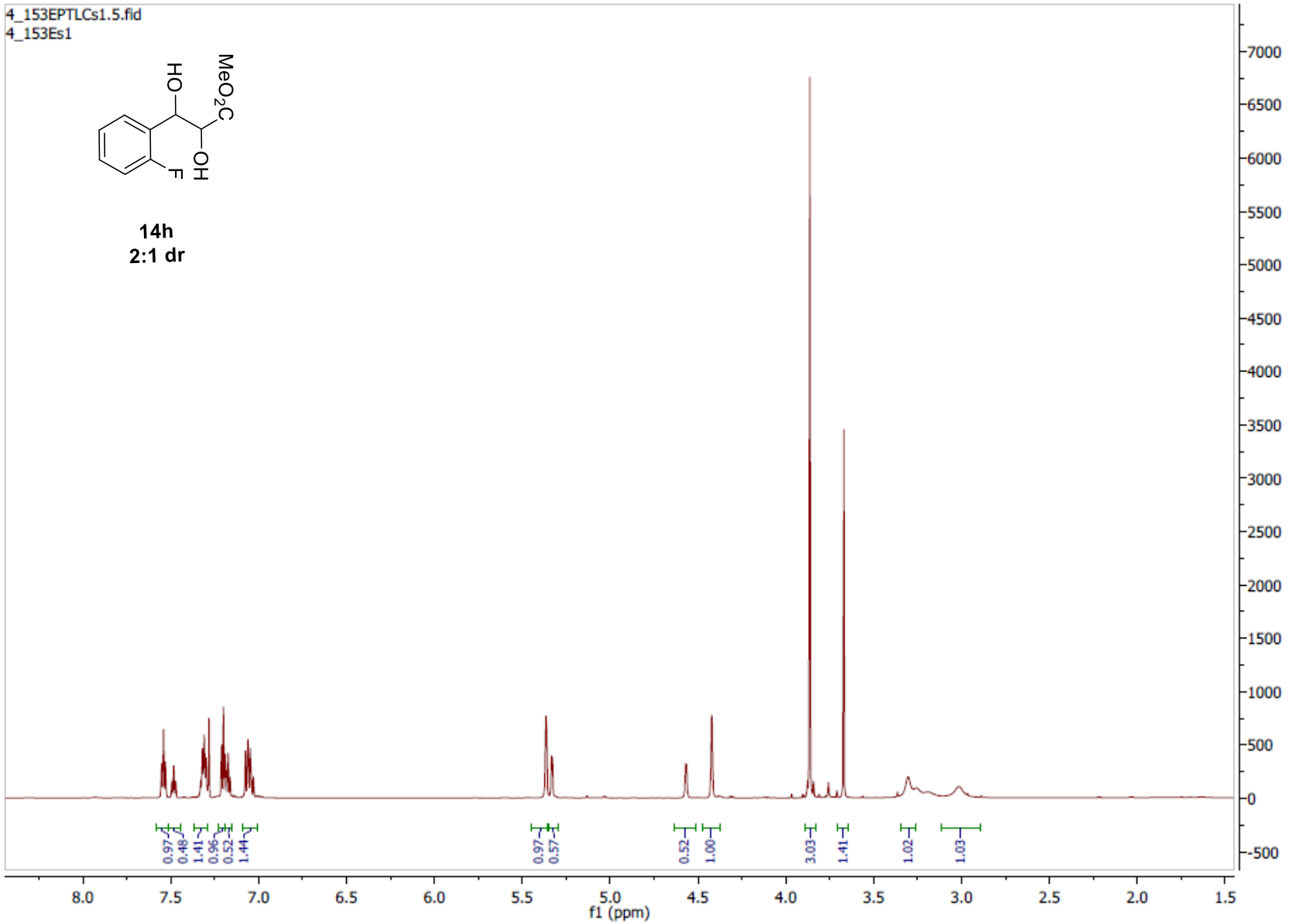

64.87
74.85
112.77
119.47
147.34
150.17
187.63
HO
OH
O
O
10s
4_47Ds2.2.fid
4_47Ds2
f1 (ppm)

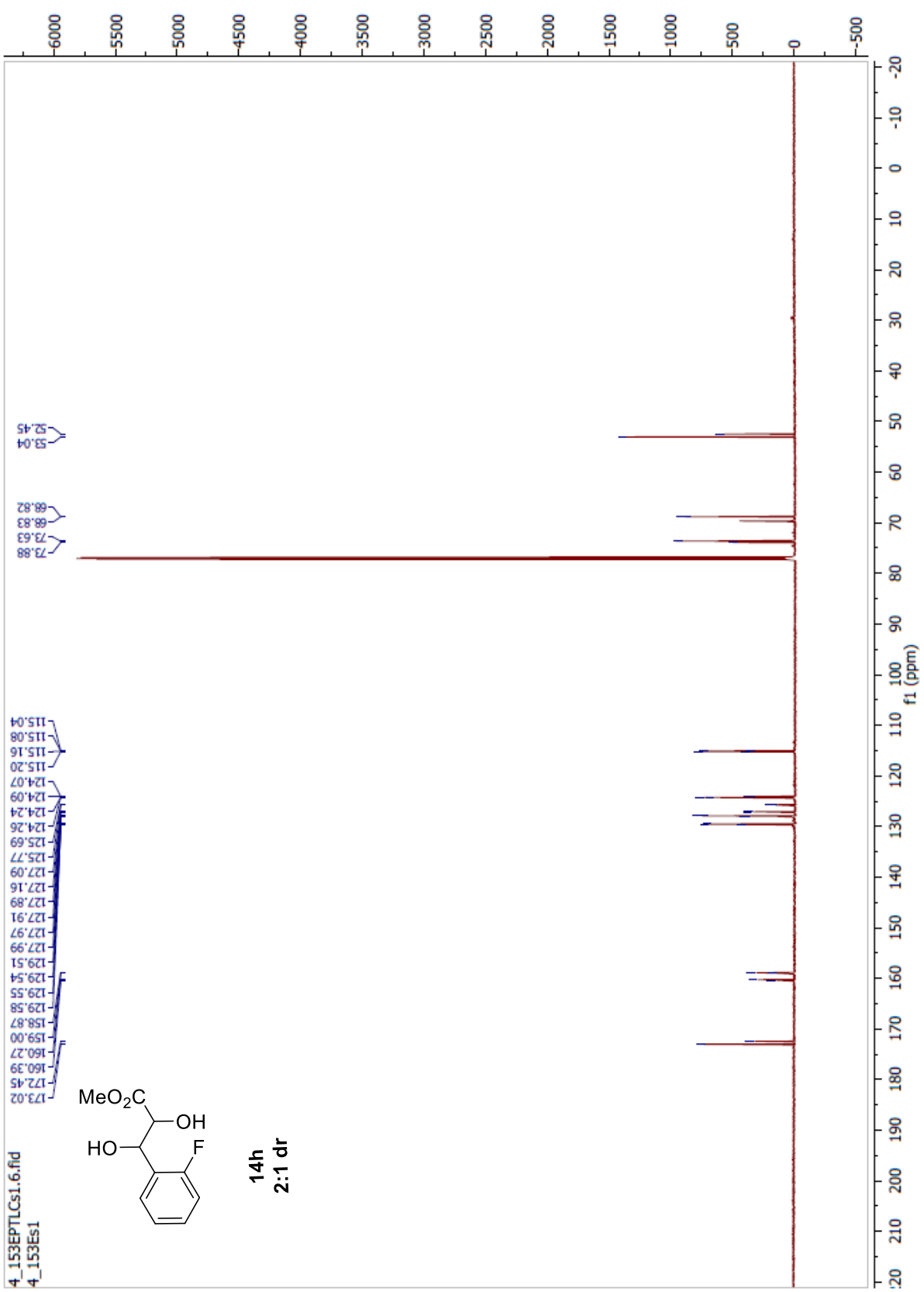

HO
OH
O
N
10ak
4_104Cs2.1.fid
4_104Cs2
f1 (ppm)
1.19
4.40
1.02
0.96
1.11
1.08
2.10
1.00

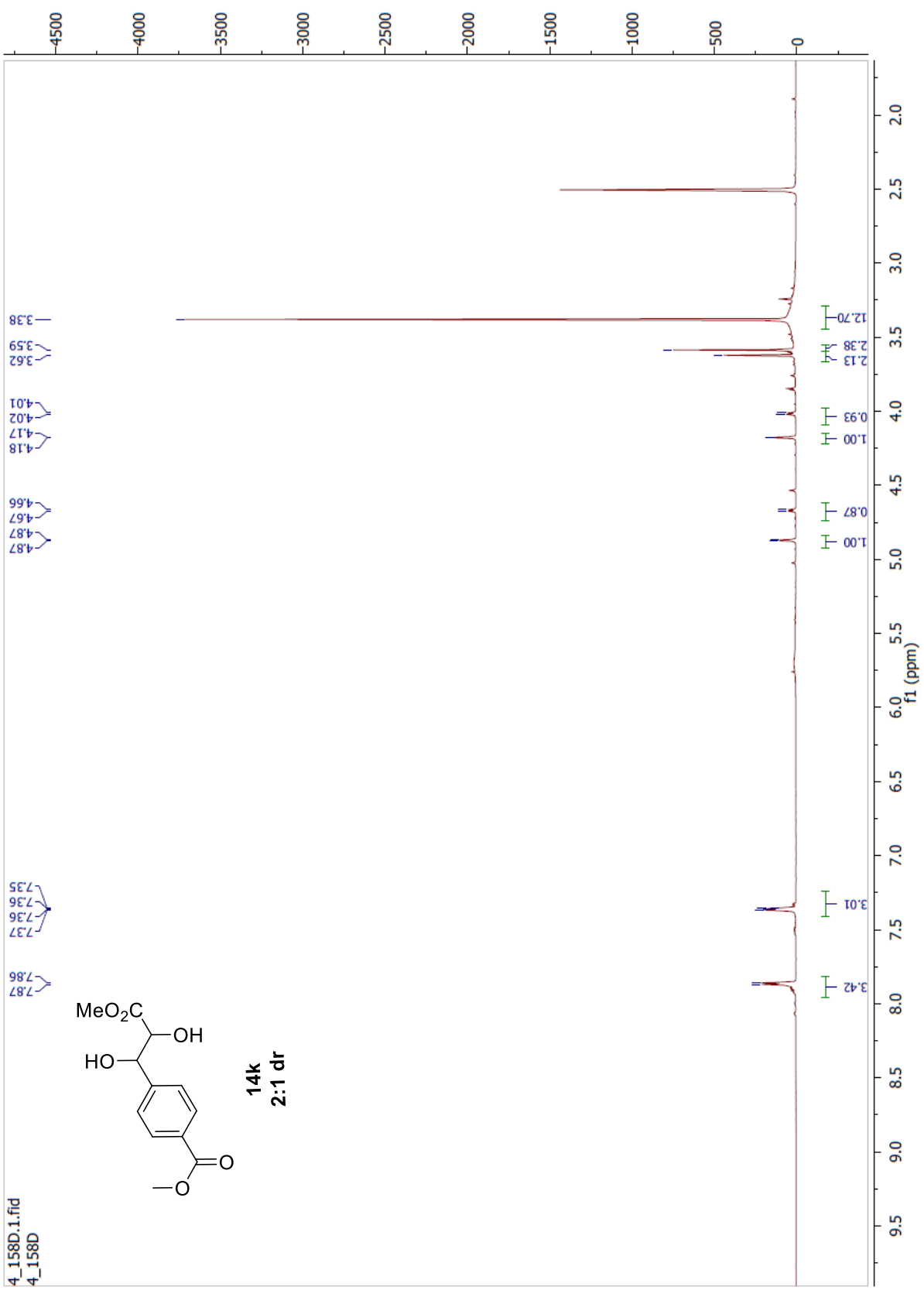

32.23
53.46
66.91
74.92
110.52
112.64
121.25
123.22
125.84
126.92
131.30
140.47
191.87
HO
OH
O
N
10ak
4_104Cs2.2.fid
4_104Cs2
f1 (ppm)

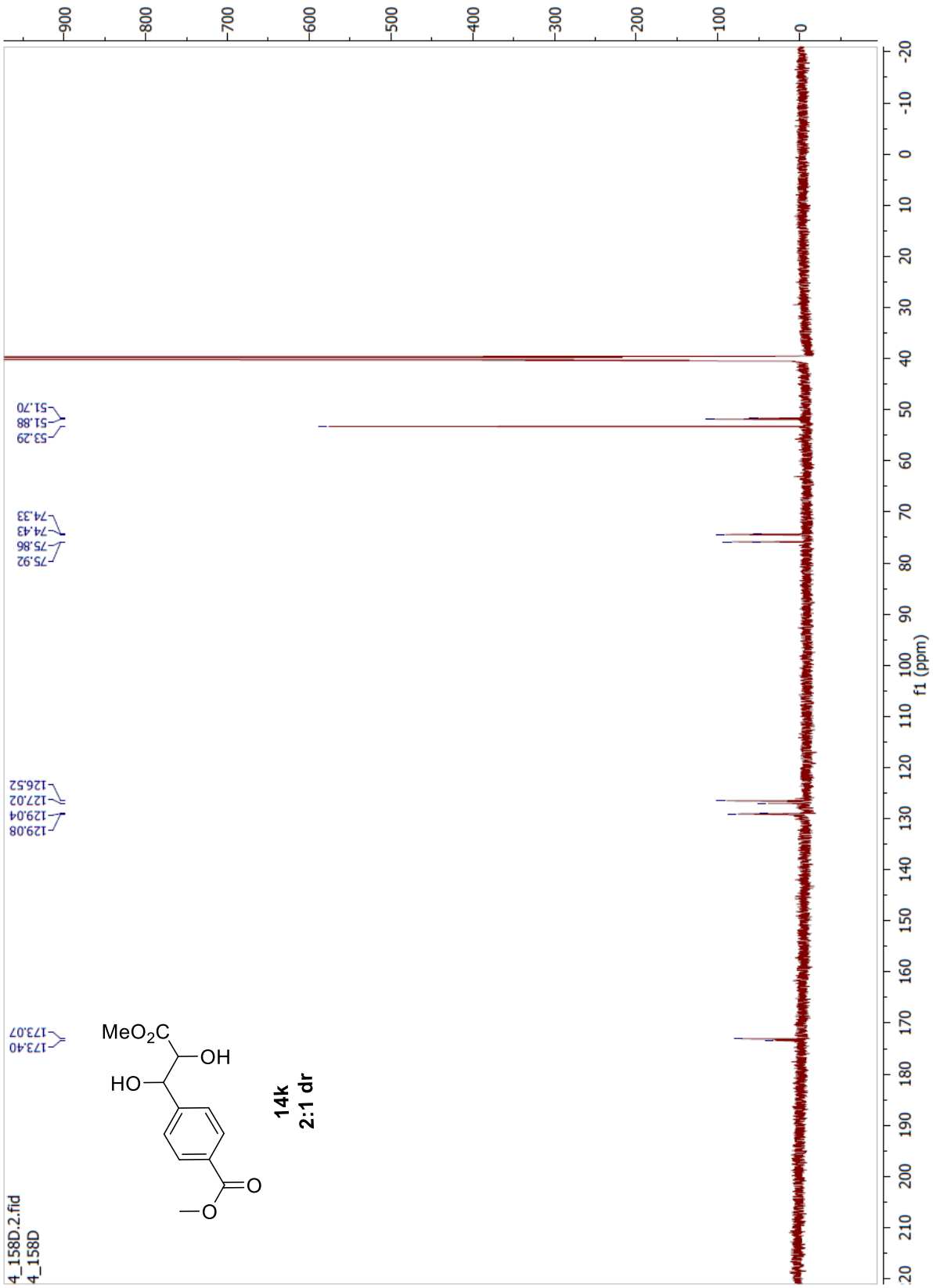

4_153DPTLCs1.5.fid
4_153Ds1
MeO2C
OH
HO
F
14g
2:1 dr
f1 (ppm)

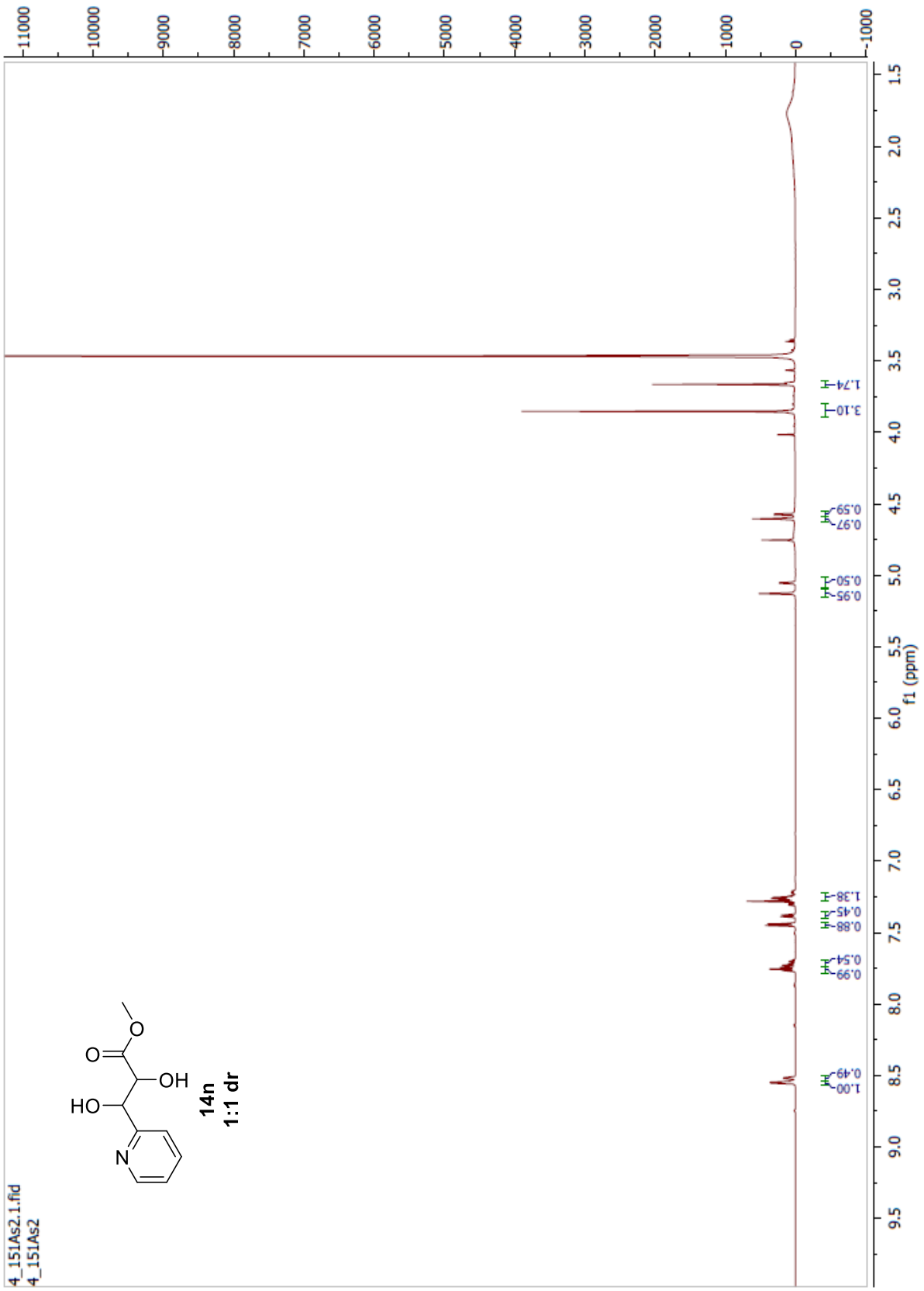

4_153DPTLCs1.6.fid
4_153Ds1
172.94
172.20
163.60
163.47
162.20
162.08
142.65
142.61
141.26
141.22
130.03
129.98
129.84
129.80
121.95
121.93
121.75
121.73
115.14
115.02
114.91
113.54
113.45
113.41
113.33
74.63
74.44
74.38
73.75
53.03
52.58
HO
MeO2C
OH
F
14g
2:1 dr
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
f1 (ppm)


4_153EPTLCs1.5.fid
4_153Es1
HO
MeO2C
OH
F
14h
2:1 dr
f1 (ppm)

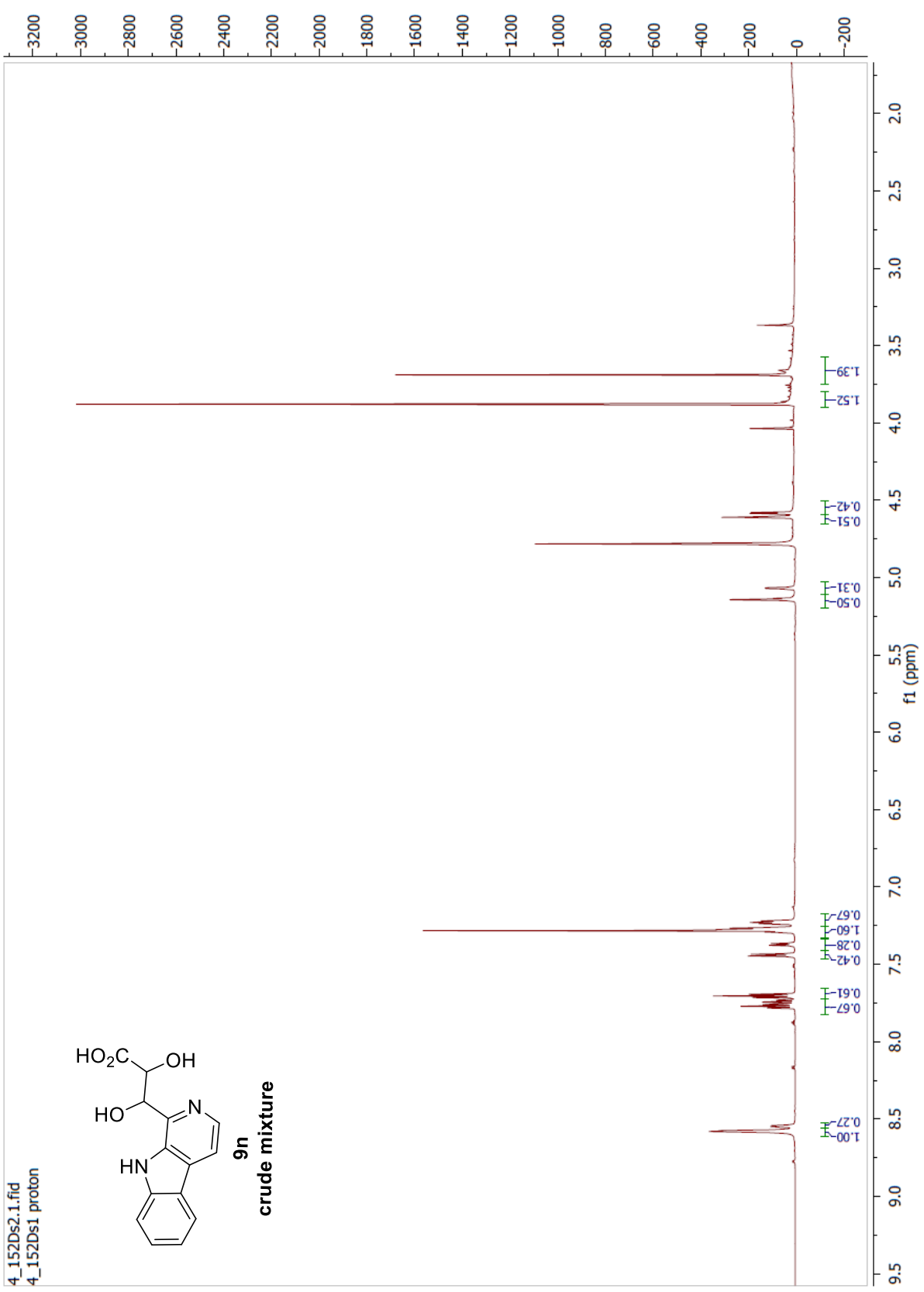

4_153EPTLCs1.6.fid
4_153Es1
14h
2:1 dr
MeO2C
OH
HO
F
f1 (ppm)

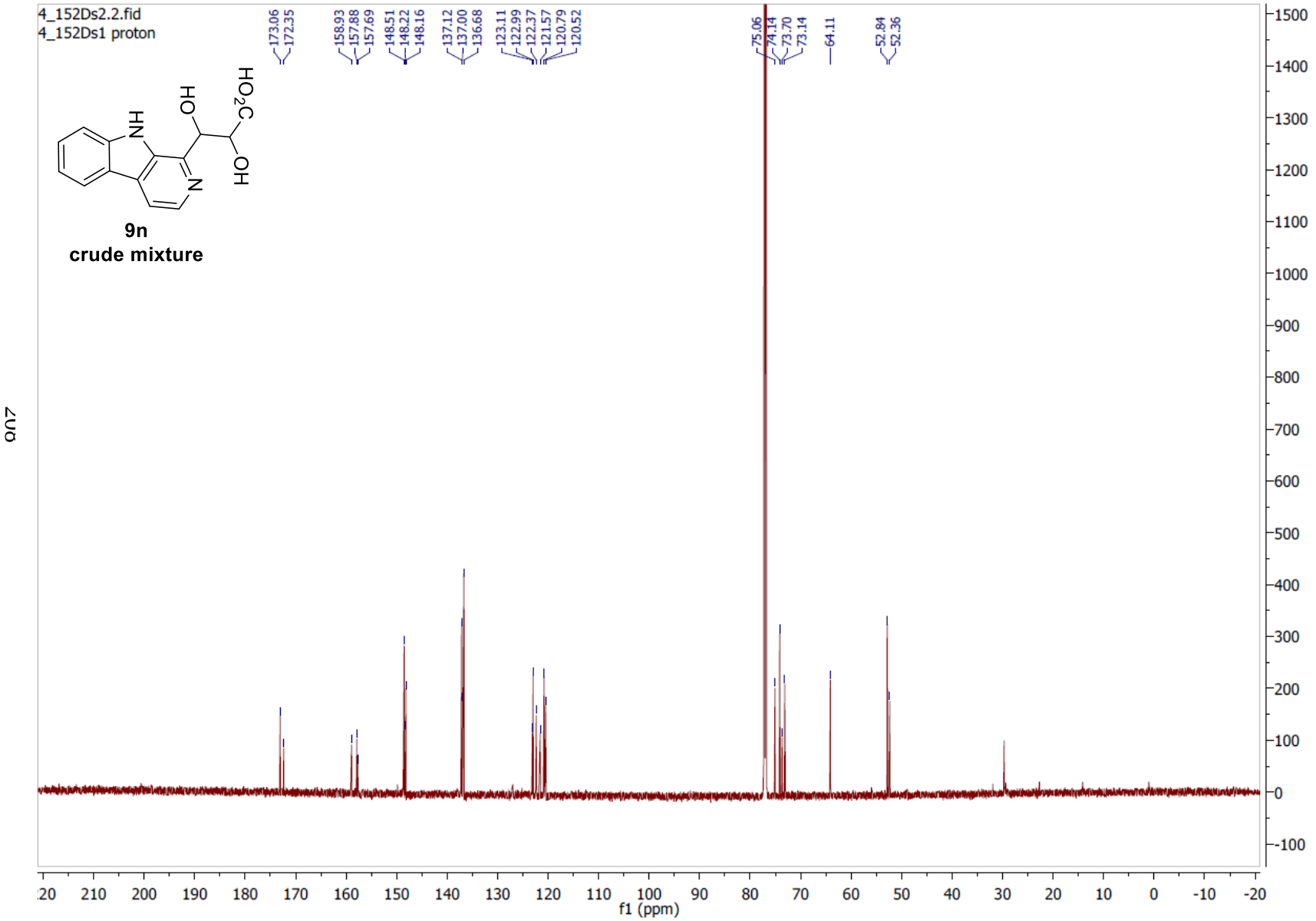

4_158D.1.fid
4_158D
14k
2:1 dr
MeO2C
OH
HO
O
O
f1 (ppm)


MeO2C
OH
HO
O
O
14k
2:1 dr
4_158D.2.fid
4_158D
f1 (ppm)

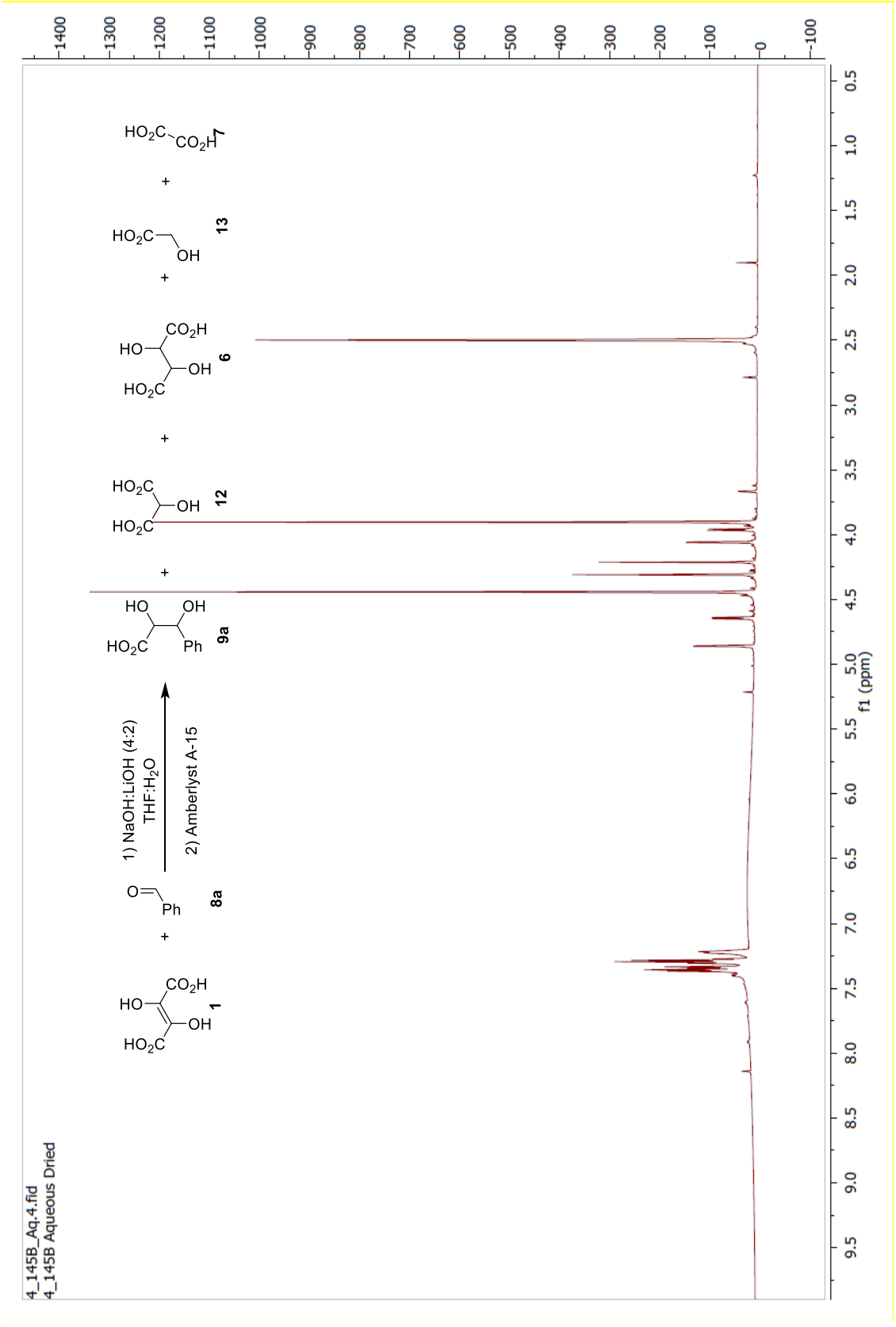

4_151As2.1.fid
4_151As2
14n
1:1 dr
HO
OH
O
O
N
1.00
0.49
0.99
0.54
0.88
0.45
1.38
0.95
0.50
0.97
0.59
3.10
1.74
f1 (ppm)

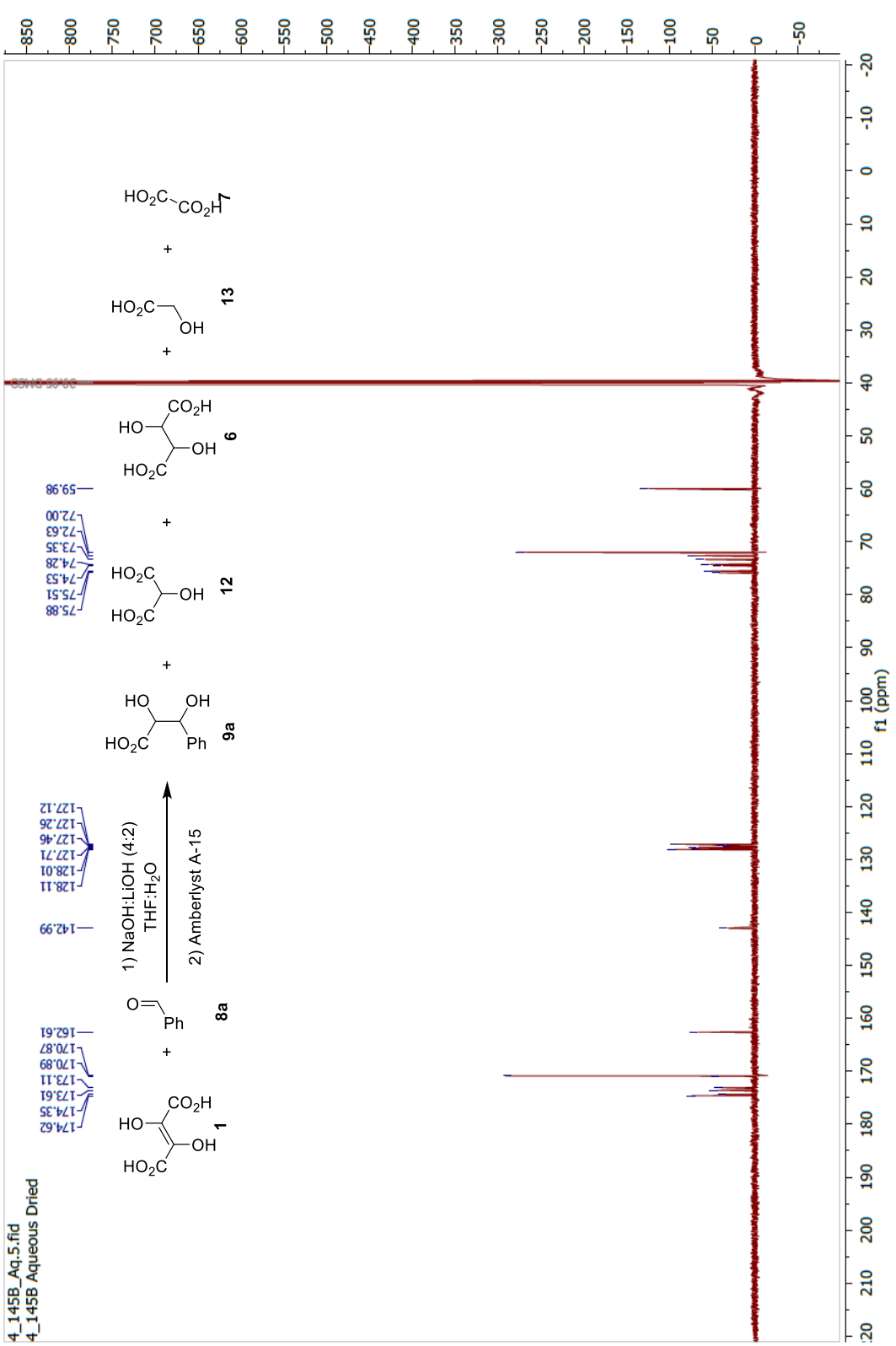
4_151As2.2.fid
4_151As2
14n
1:1 dr
HO
OH
O
O
N
173.03
172.33
158.03
157.84
148.42
148.11
137.09
136.95
122.99
122.90
121.50
120.84
75.04
74.10
73.91
73.30
52.73
52.23
f1 (ppm)

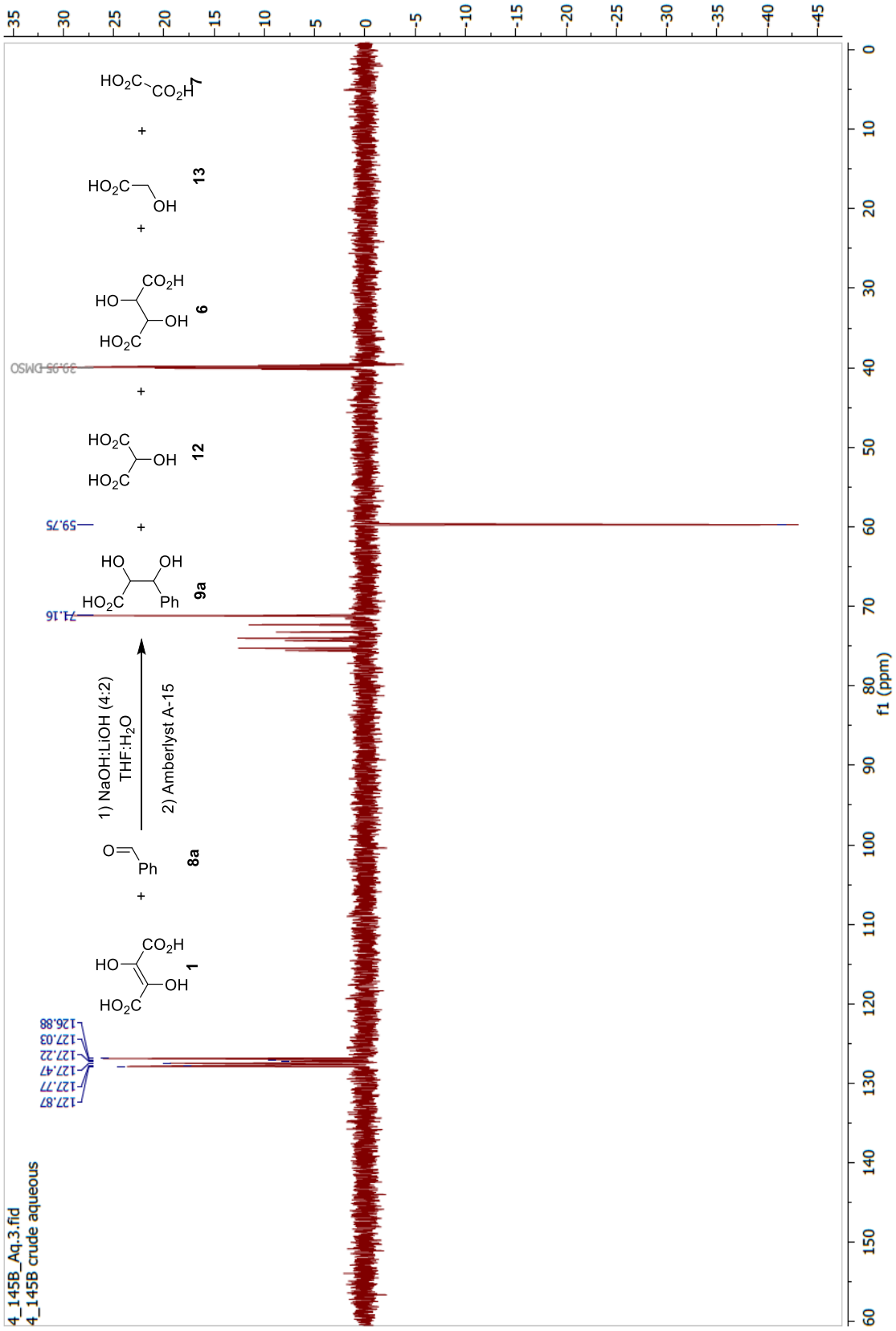

4_152Ds2.1.fid
4_152Ds1 proton
HO2C
OH
HO
N
HN
9n
crude mixture
f1 (ppm)

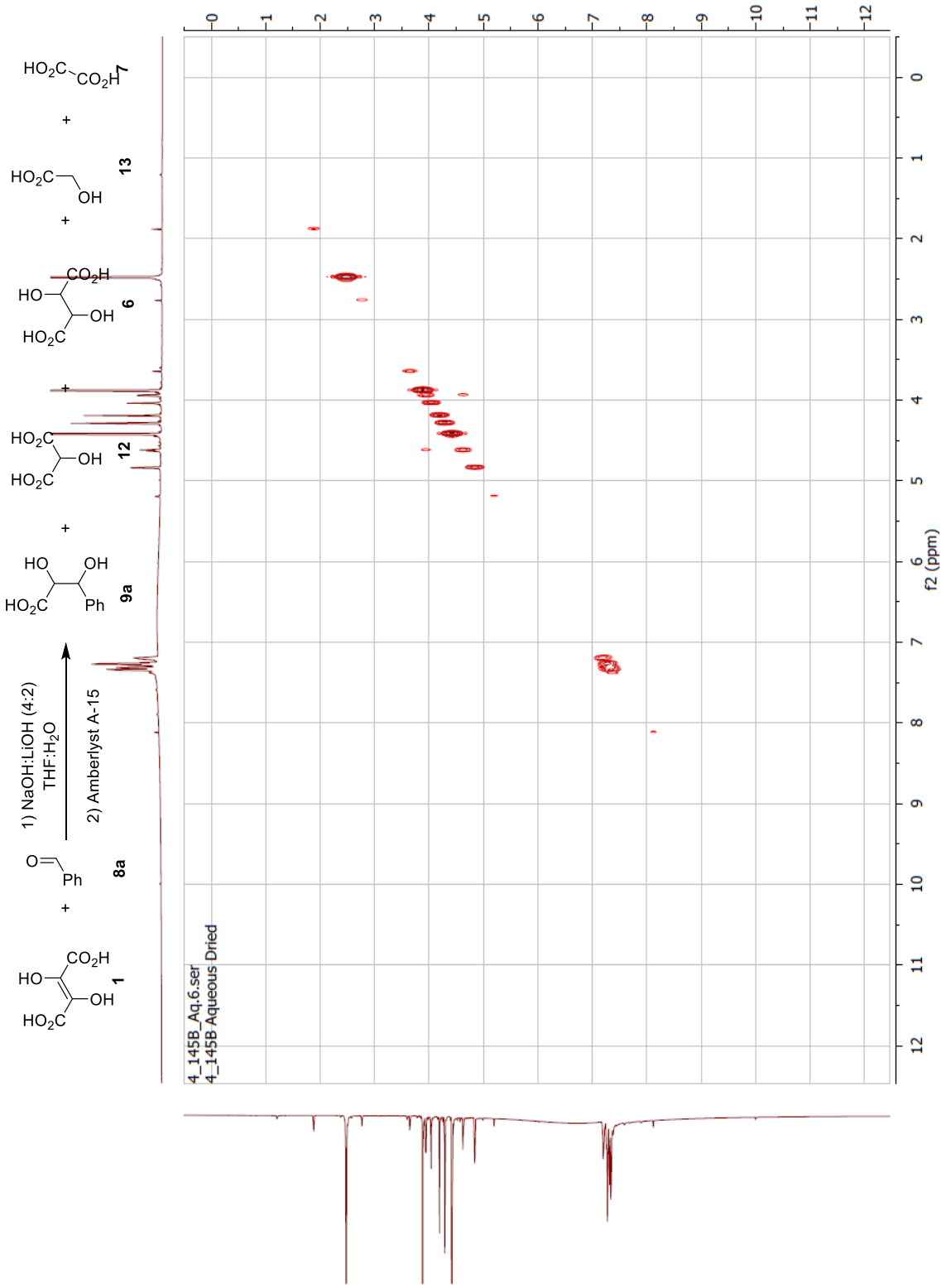

4_152Ds2.2.fid
4_152Ds1 proton
173.06
172.35
158.93
157.88
157.69
148.51
148.22
148.16
137.12
137.00
136.68
123.11
122.99
122.37
121.57
120.79
120.52
75.06
74.14
73.70
73.14
64.11
52.84
52.36
NH
OH
HO2C
OH
N
9n
crude mixture
f1 (ppm)

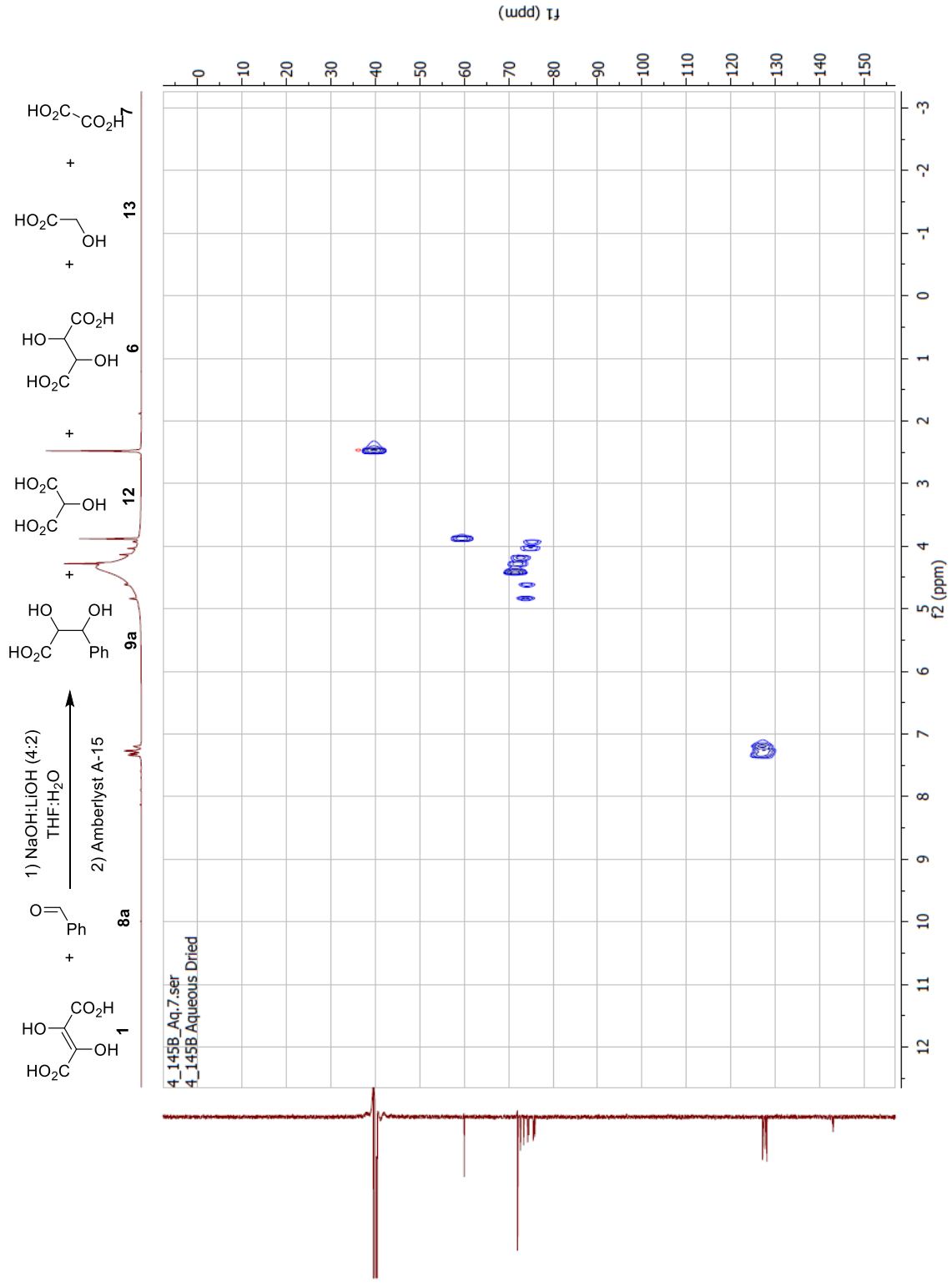
DHF/Benzaldehyde Analysis NMRs and Controls



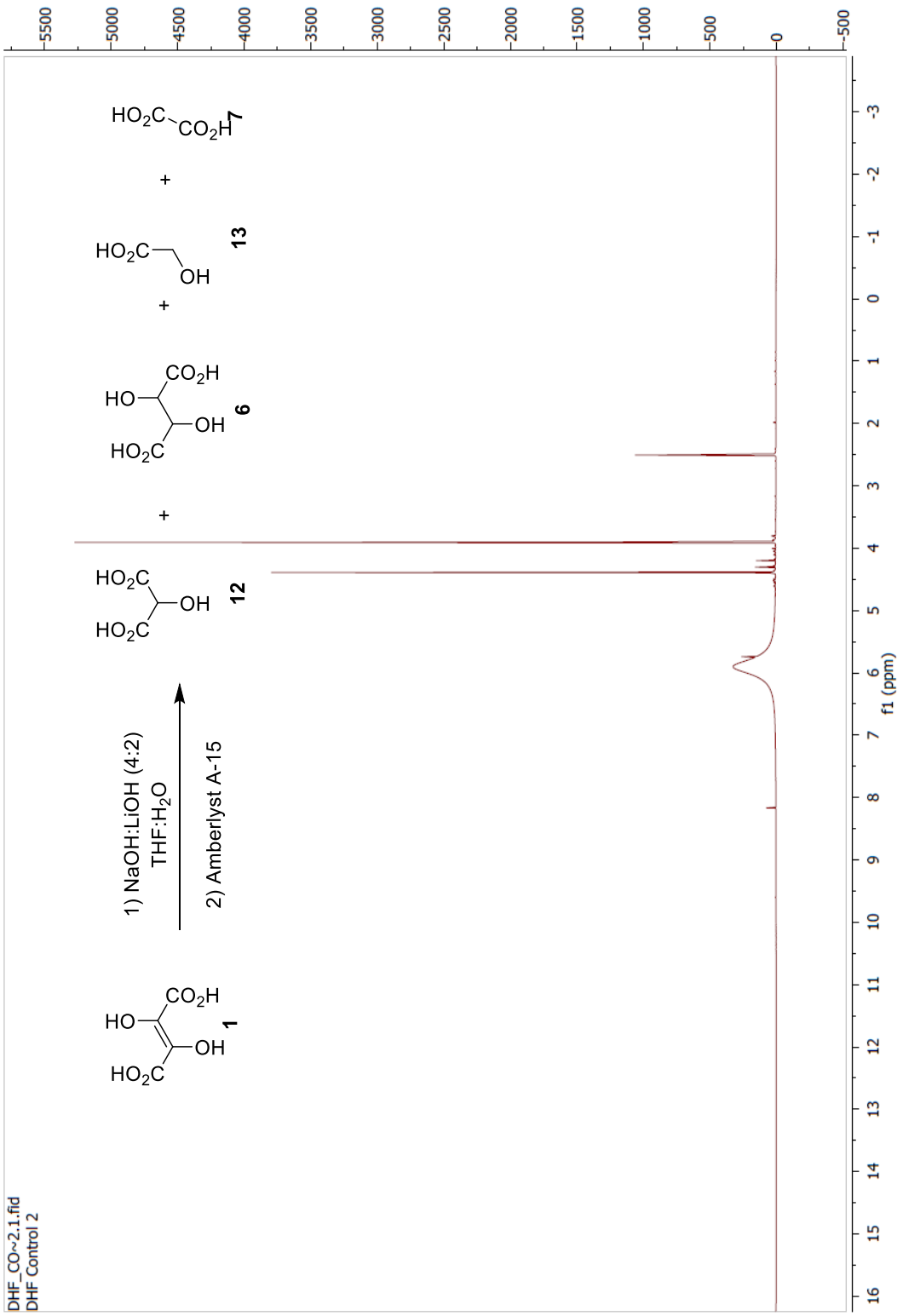

4_145B_Aq.5.fid
4_145B Aqueous Dried
1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
f1 (ppm)

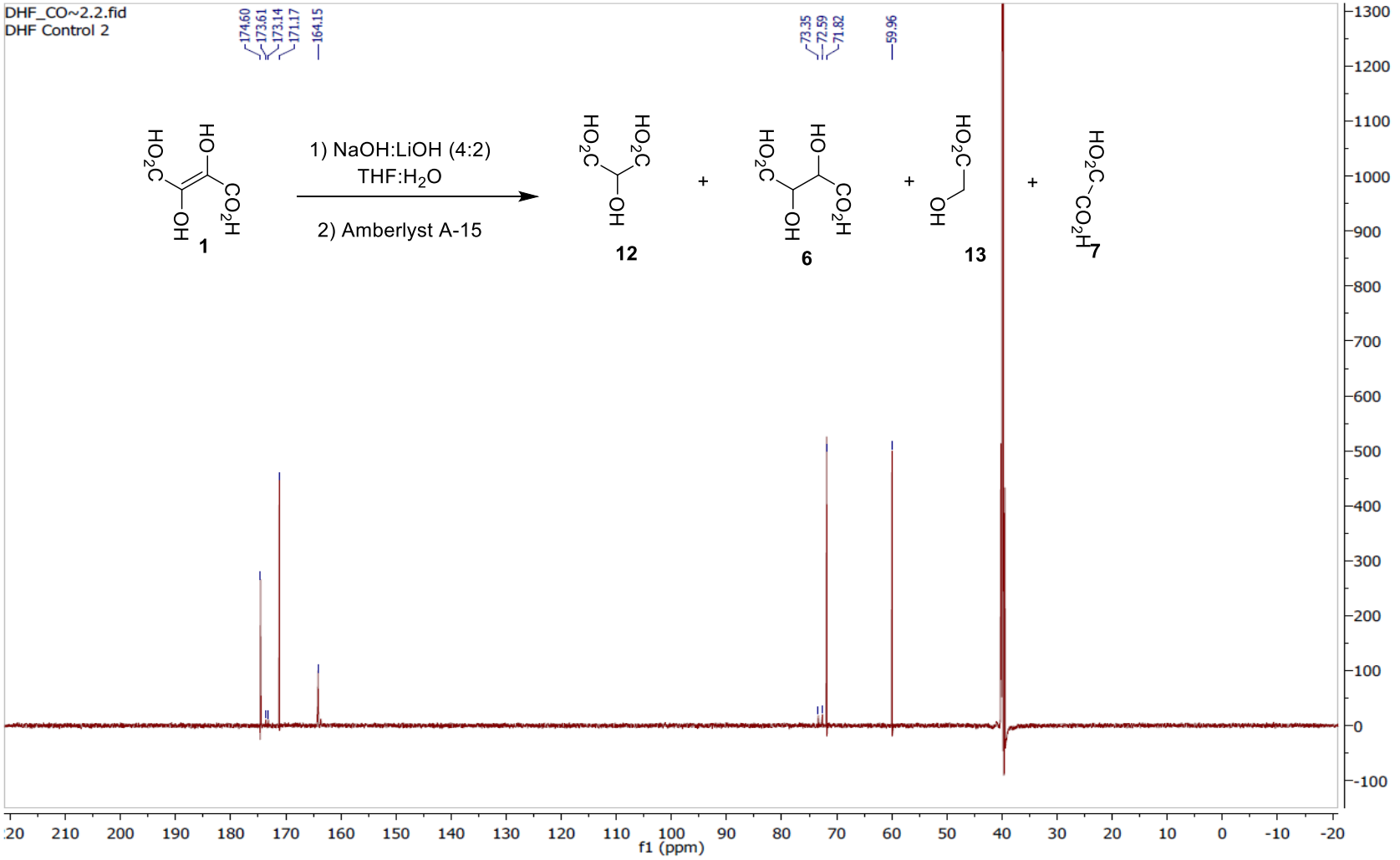

4_145B_Aq.3.fid
4_145B crude aqueous
f1 (ppm)
1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
8a
1
9a
6
12
13
7
39.95 DMSO
59.75
71.16
127.87
127.77
127.47
127.22
127.03
126.88

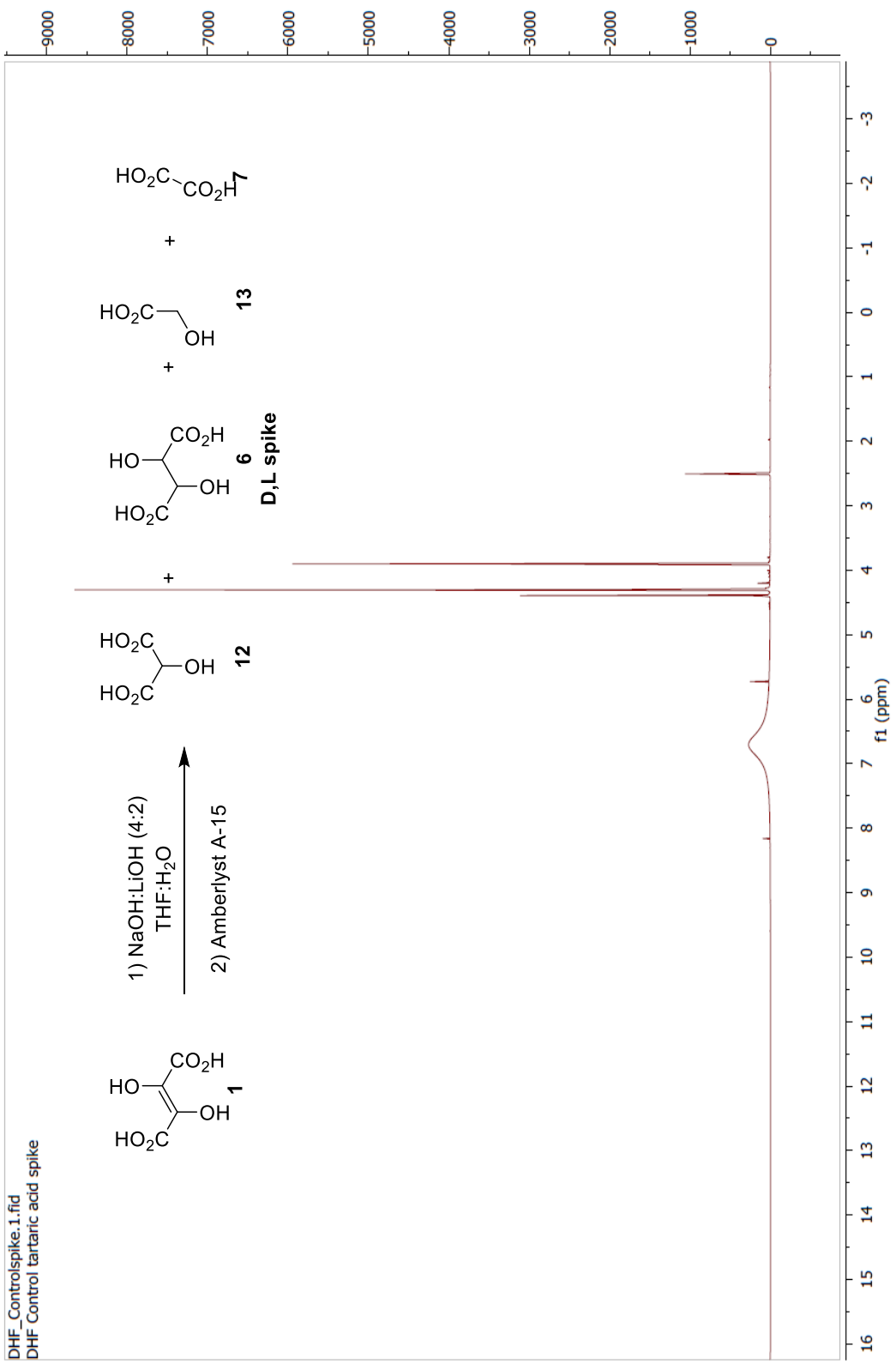

1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
1
8a
9a
12
6
13
7
4_145B_Aq,6.ser
4_145B Aqueous Dried
f2 (ppm)

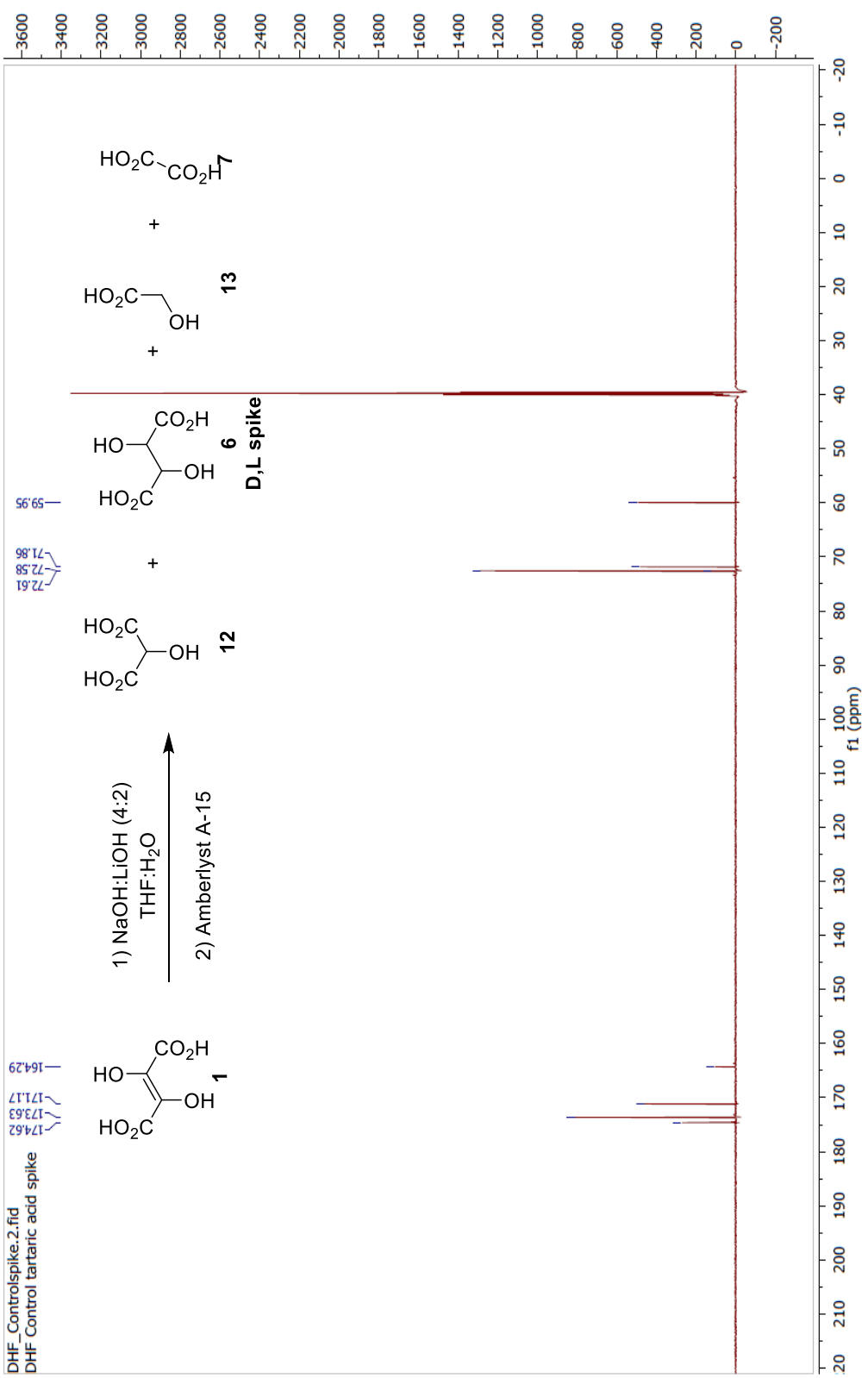

1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
1
8a
9a
12
6
13
7
4_145B_Aq.7.ser
4_145B Aqueous Dried
f1 (ppm)
f2 (ppm)

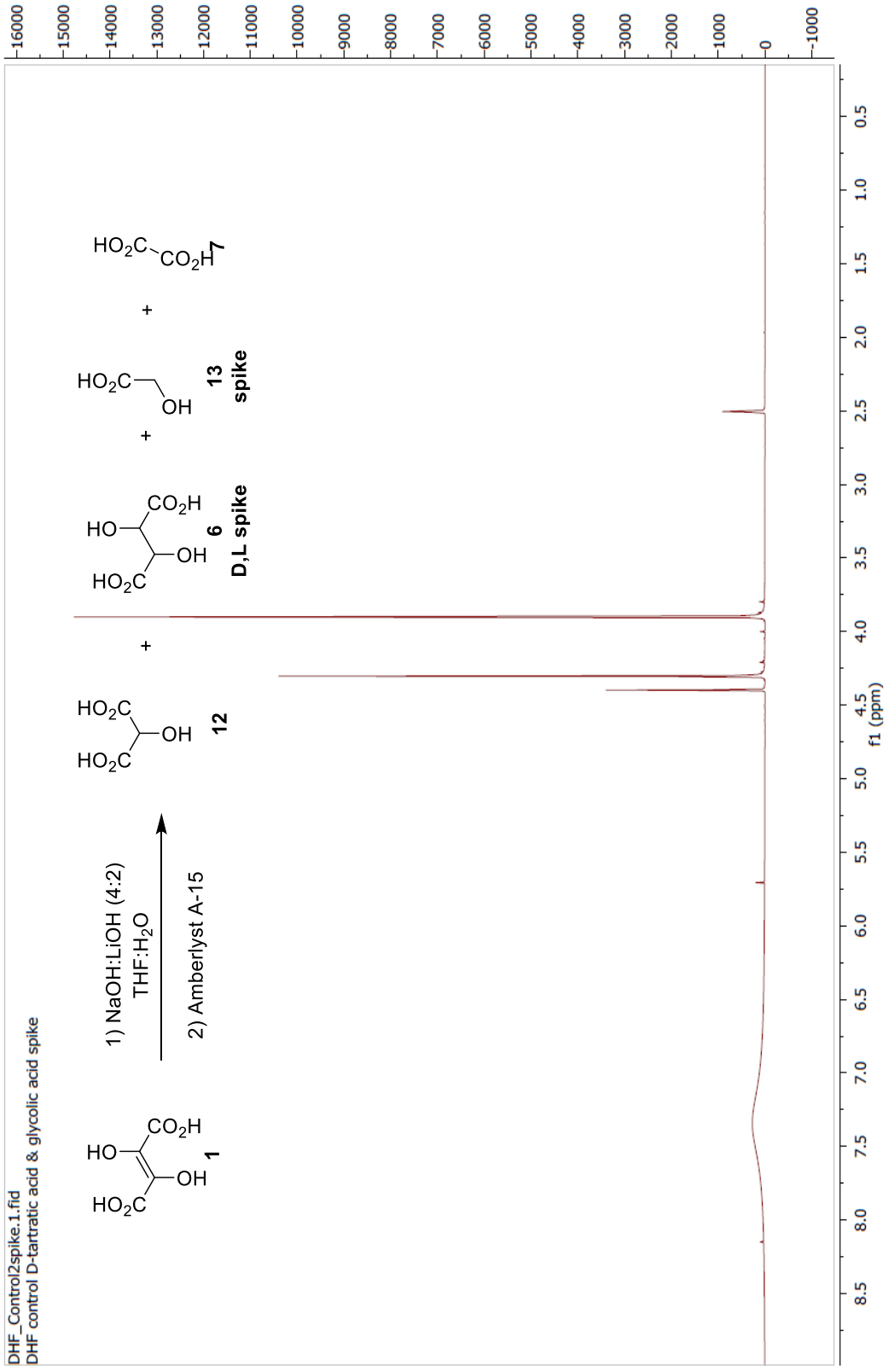
DHF Control Reaction

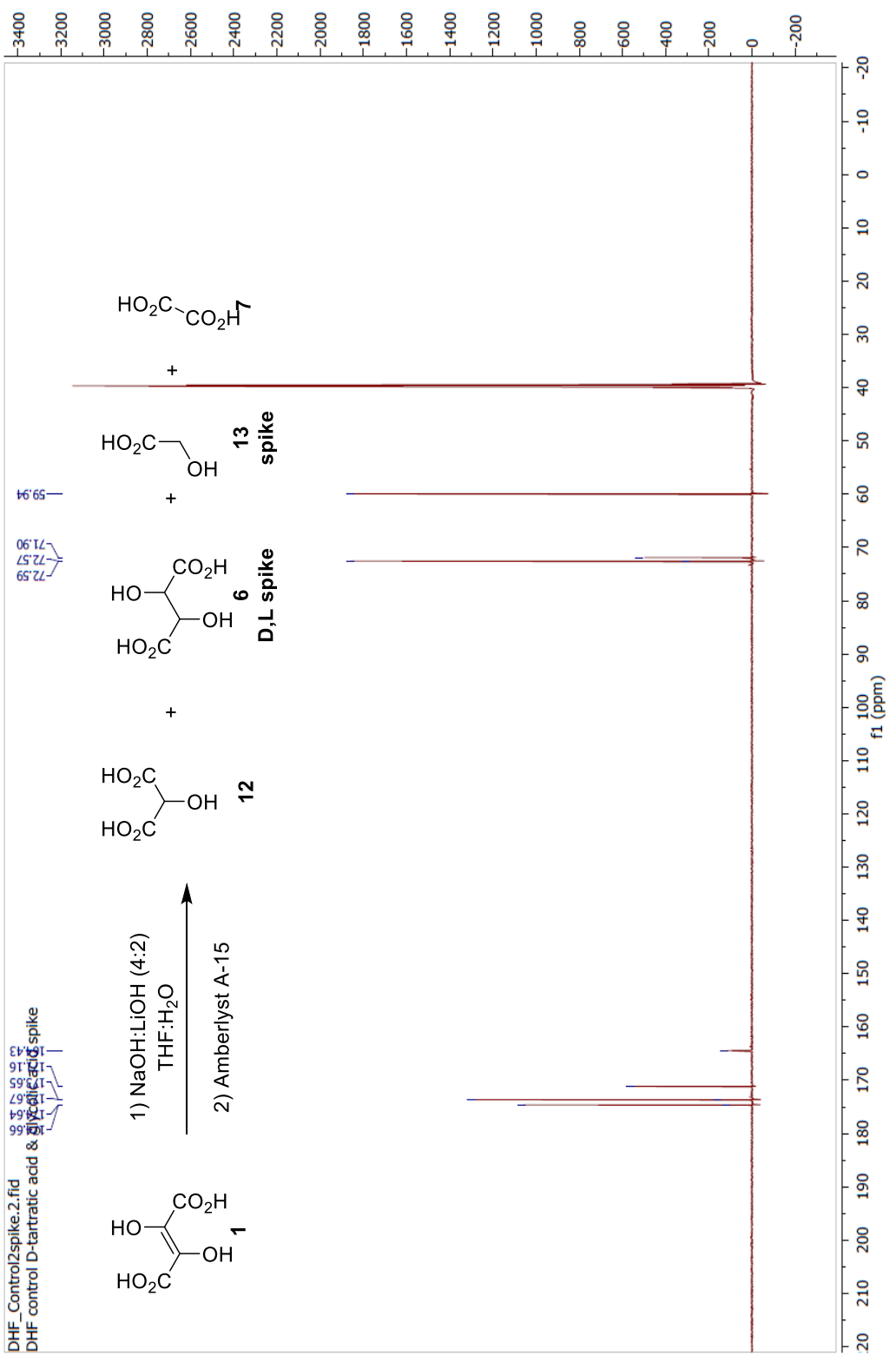


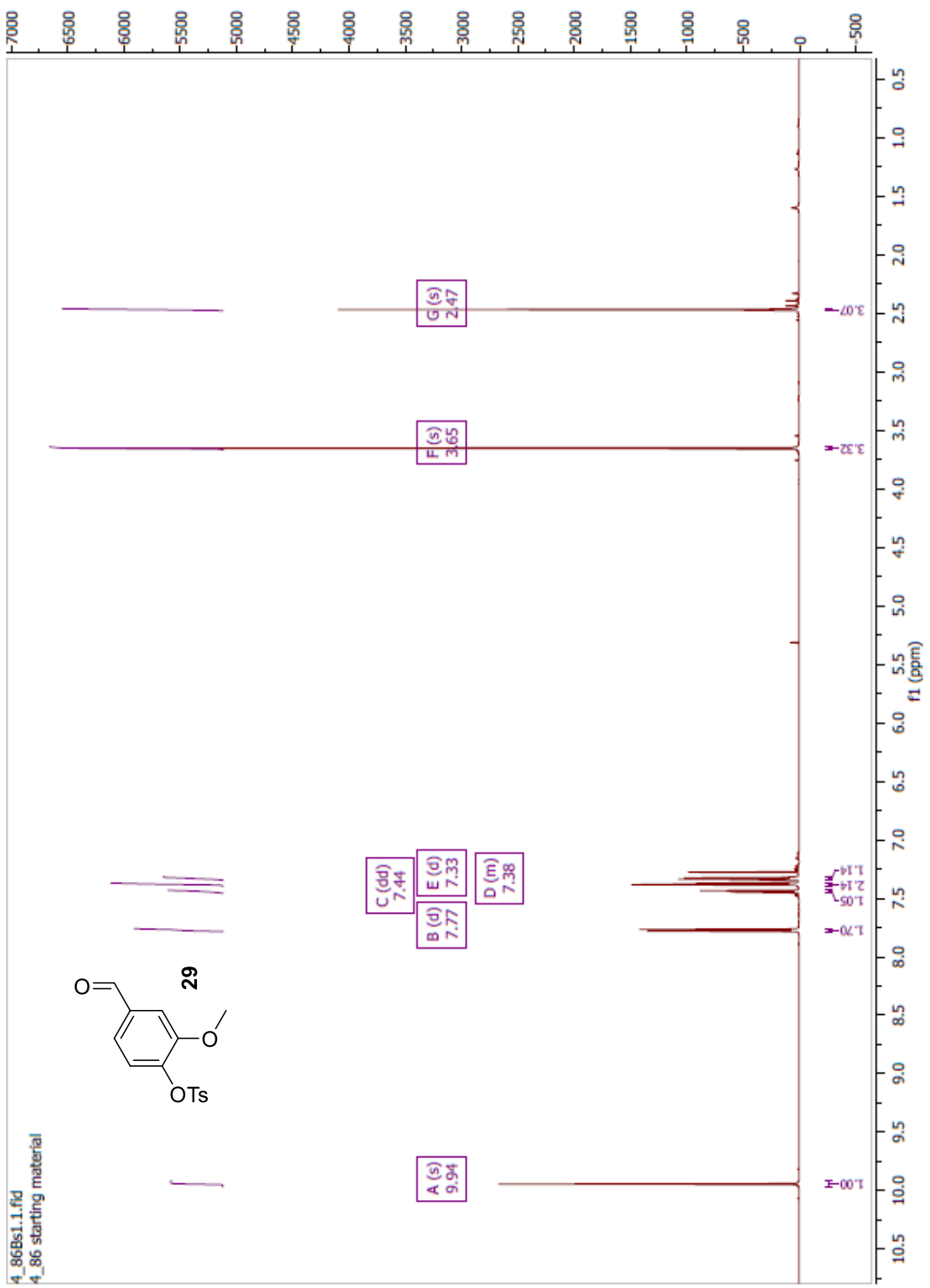

DHF_CO~2.2.fid
DHF Control 2
174.60
173.61
173.14
171.17
164.15
73.35
72.59
71.82
59.96
1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
1
12
6
13
7
f1 (ppm)

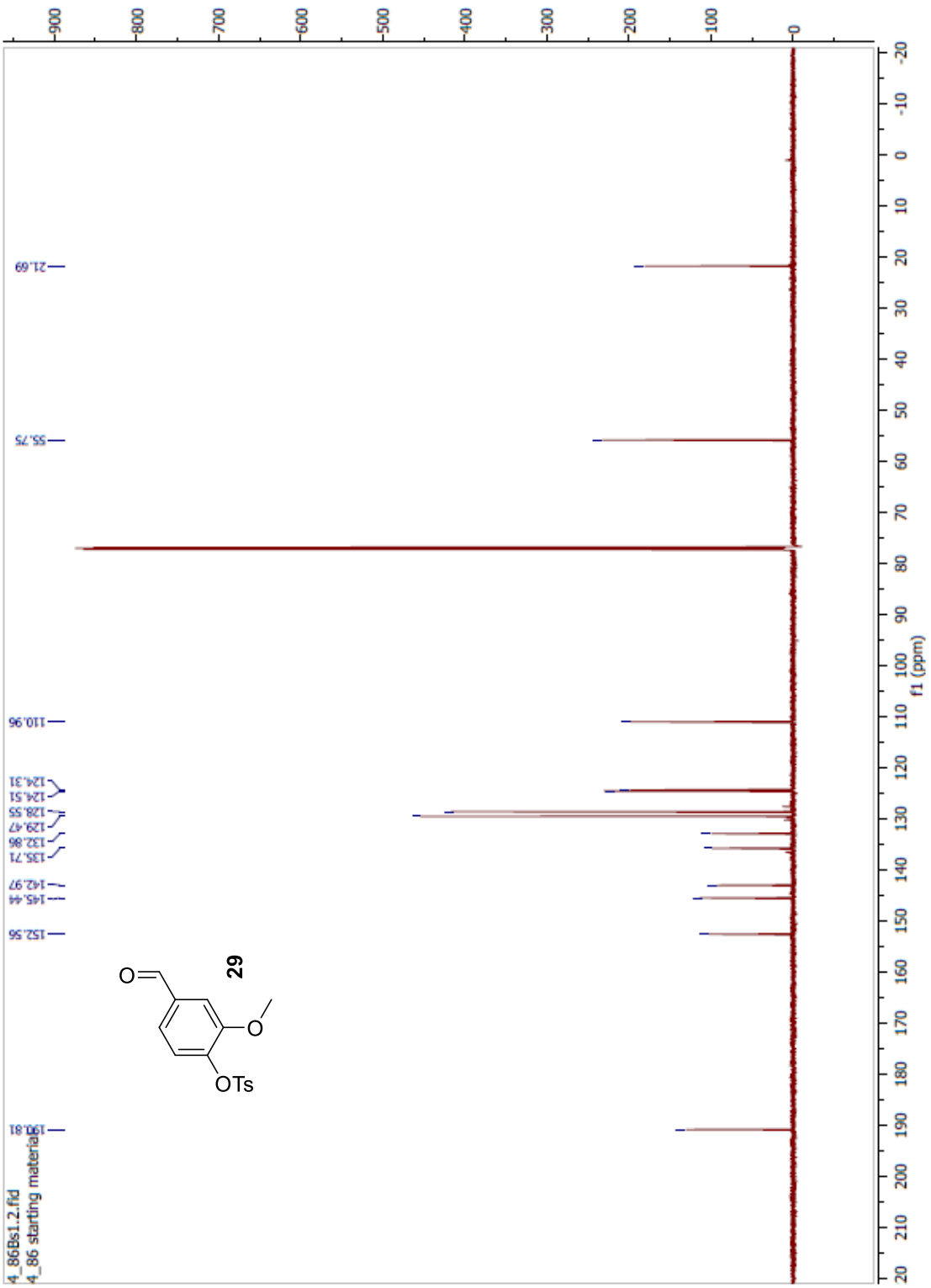

DHF_Controlspike.1.fid
DHF Control tartaric acid spike
1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
1
12
13
6
D,L spike
7
f1 (ppm)

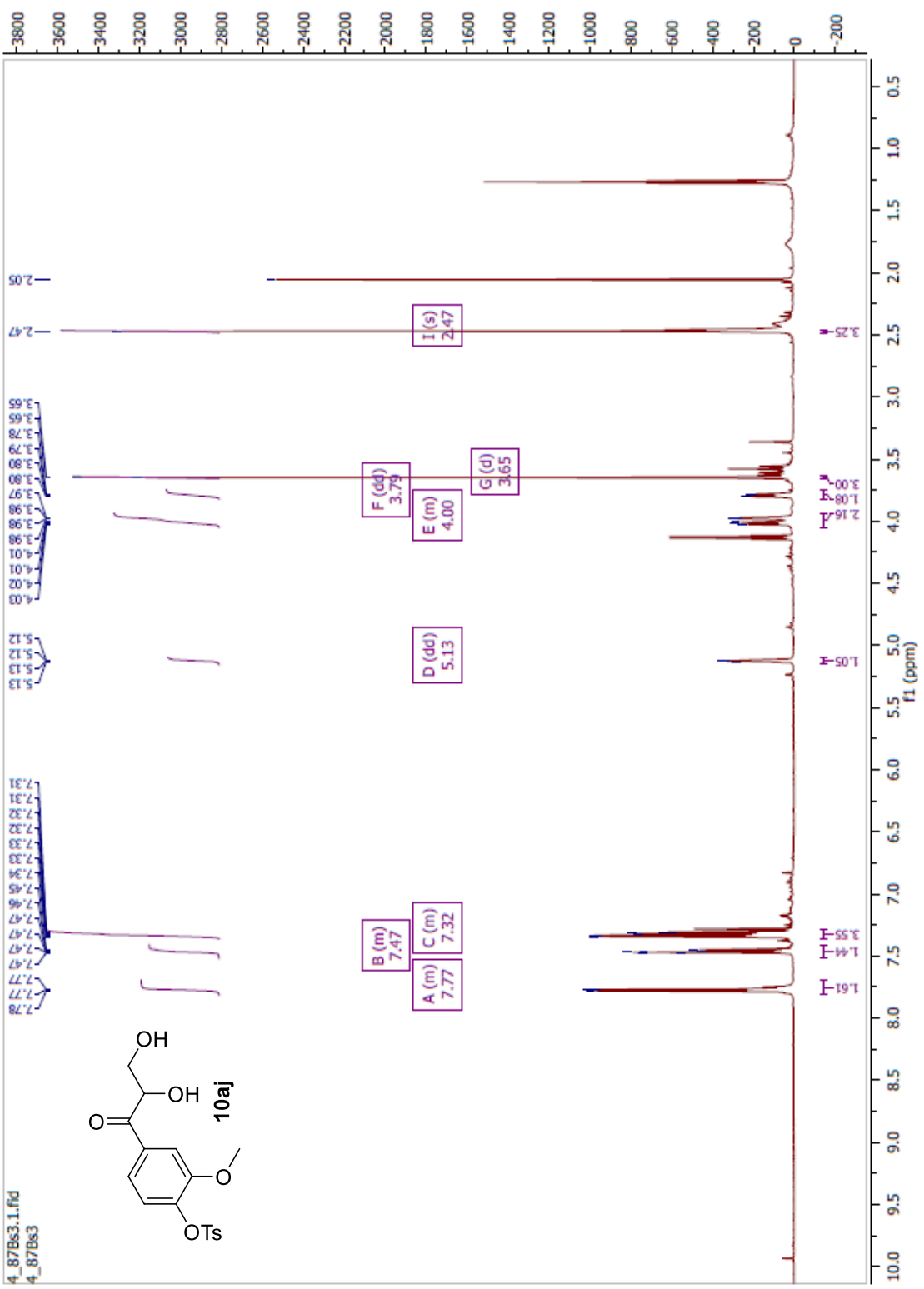

DHF_Controlspike.2.fid
DHF Control tartaric acid spike
1
1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
12
13
6
D,L spike
7
f1 (ppm)

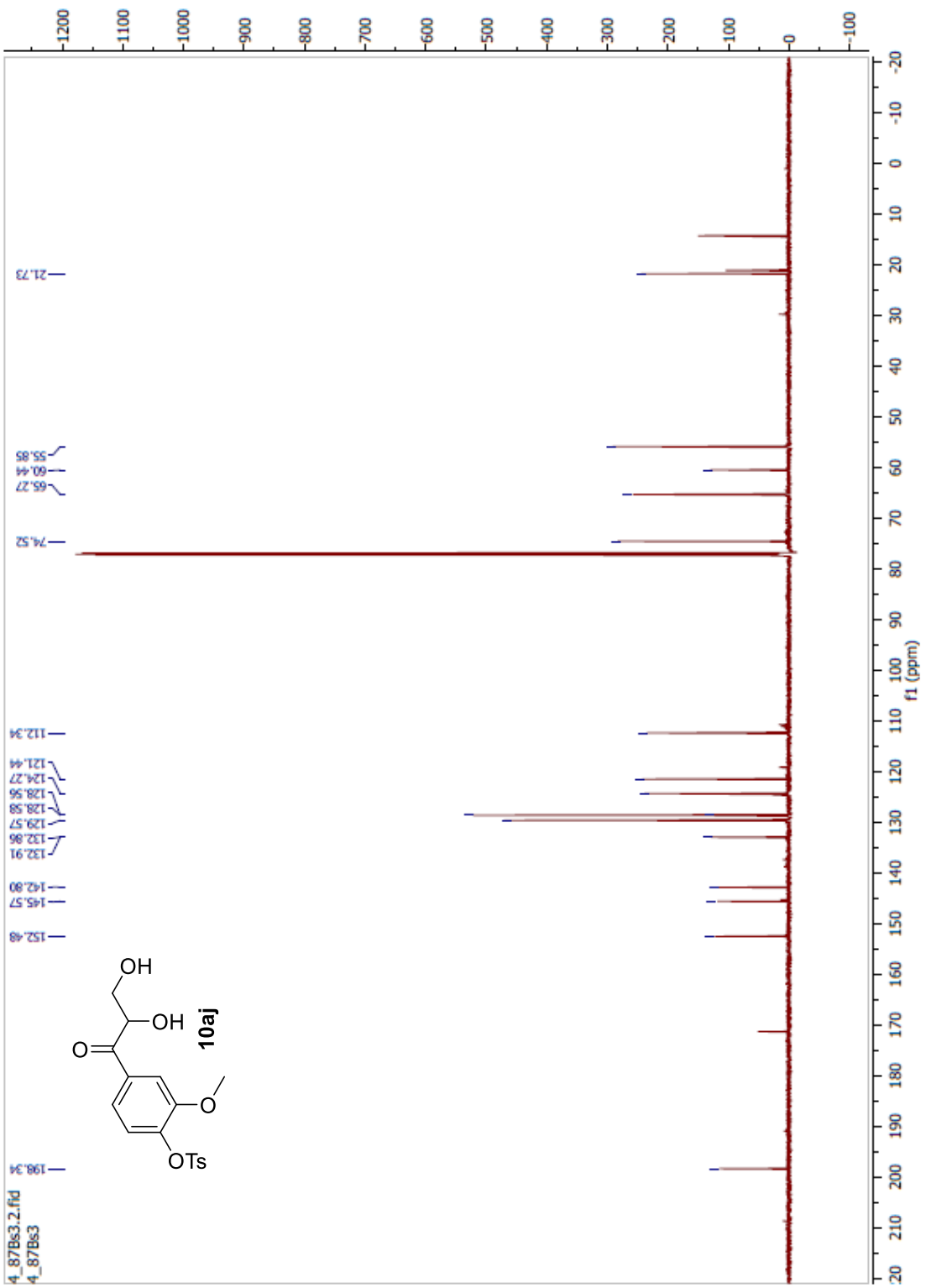

DHF_Control2spike.1.fid
DHF control D-tartratic acid & glycolic acid spike
1
1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
12
6
D,L spike
13
spike
7
f1 (ppm)

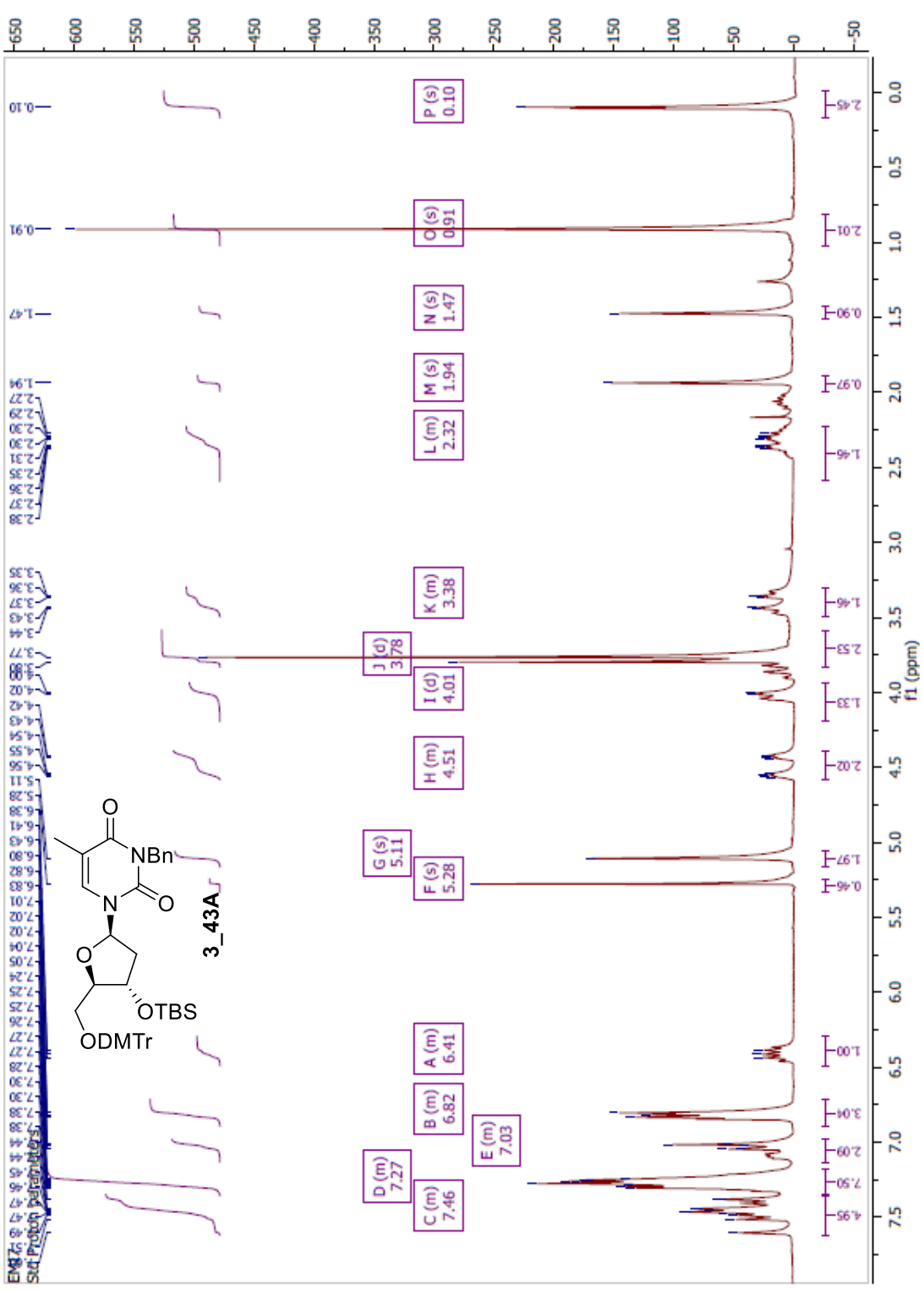

DHF_Control2spike.2.fid
DHF control D-tartratic acid & DHF spike
1) NaOH:LiOH (4:2)
THF:H2O
2) Amberlyst A-15
1
12
6
D,L spike
13
spike
7
f1 (ppm)

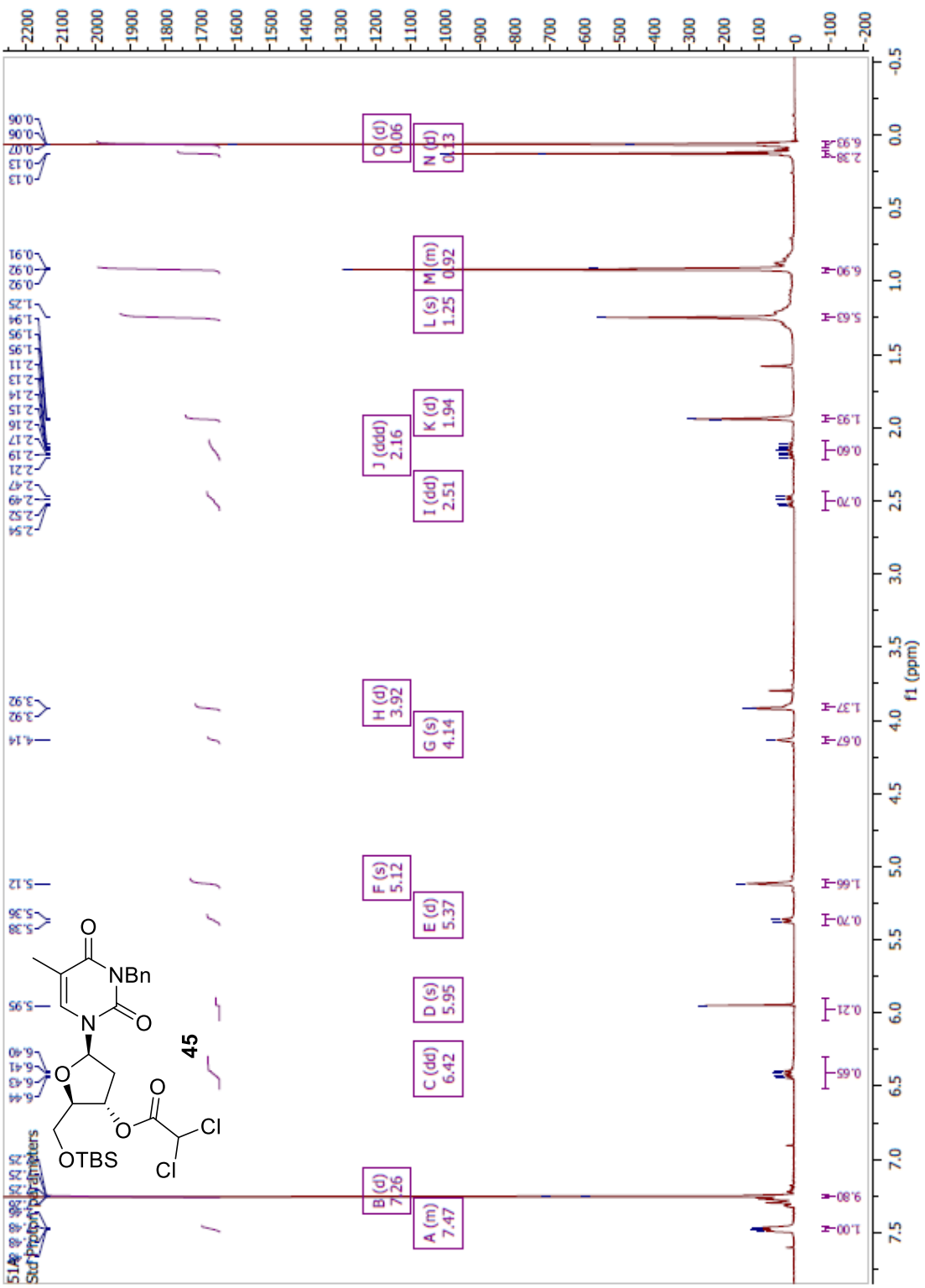

4_86Bs1.1.fid
4_86 starting material
A (s) 9.94
B (d) 7.77
C (dd) 7.44
D (m) 7.38
E (d) 7.33
F (s) 3.65
G (s) 2.47
1.00
1.70
1.05
2.14
1.14
3.32
3.07
f1 (ppm)
29
O
O
OTs

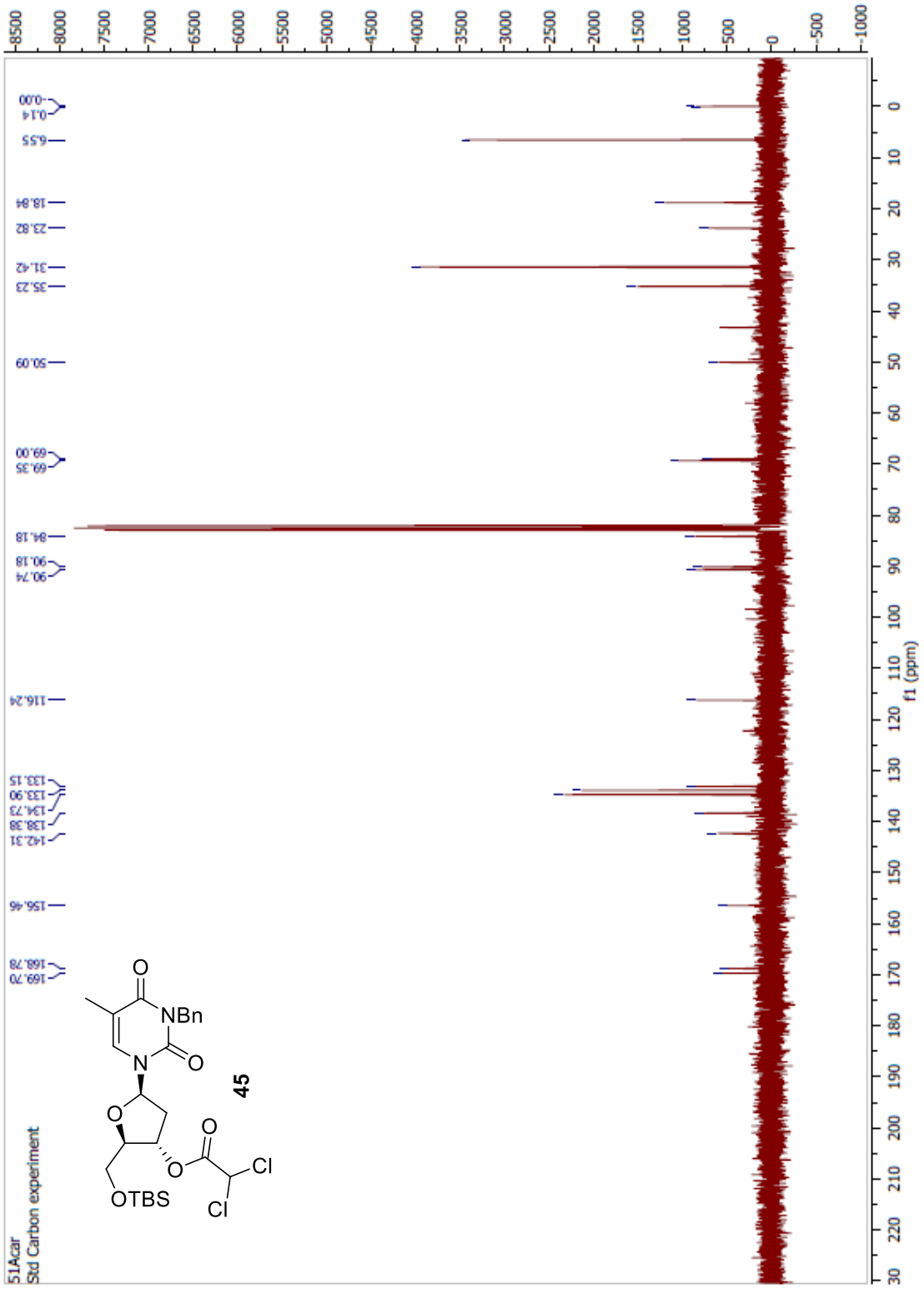

21.69
55.75
110.96
124.31
124.51
128.55
129.47
132.86
135.71
142.97
145.44
152.56
190.81
4_86Bs1.2.fid
4_86 starting material
f1 (ppm)
29
O
O
OTs

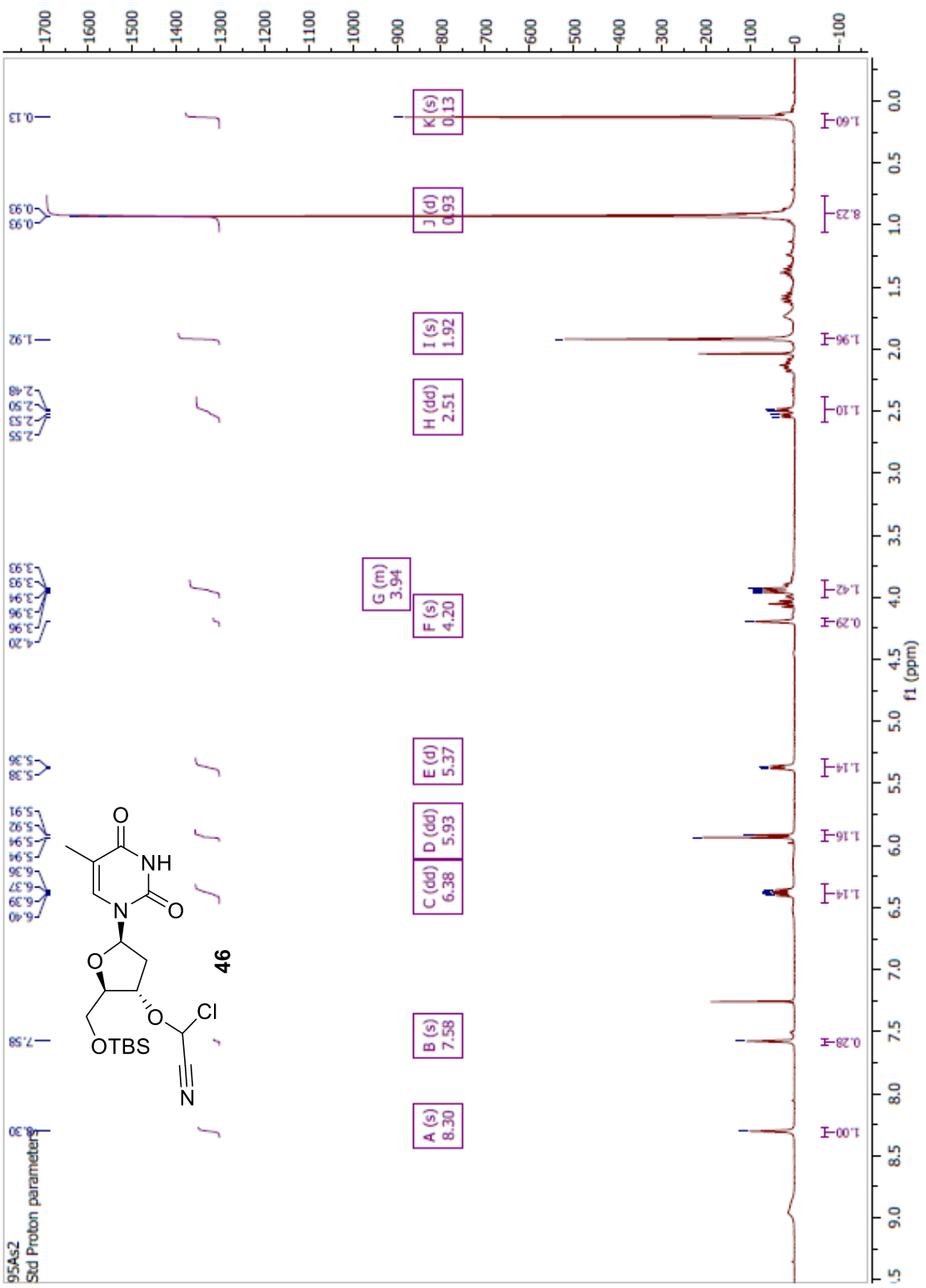

4_87Bs3.1.fid
4_87Bs3
10aj
OH
OH
O
O
OTs
A (m) 7.77
B (m) 7.47
C (m) 7.32
D (dd) 5.13
E (m) 4.00
F (dd) 3.79
G (d) 3.65
I (s) 2.47
f1 (ppm)

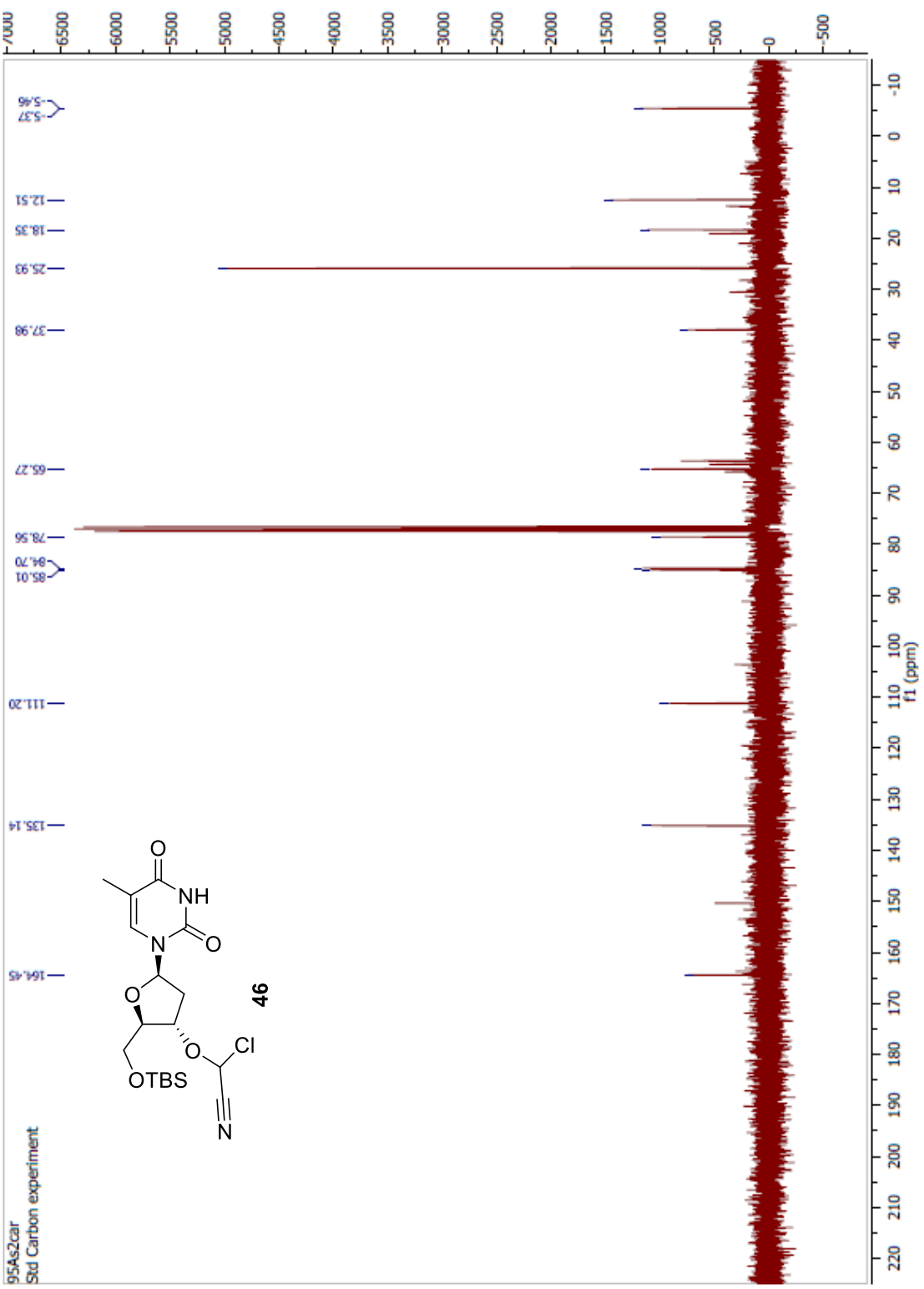

21.73
55.85
60.44
65.27
74.52
112.34
121.44
124.27
128.56
128.58
129.57
132.86
132.91
142.80
145.57
152.48
198.34
OH
OH
O
O
OTs
10aj
4_87Bs3.2.fid
4_87Bs3
f1 (ppm)

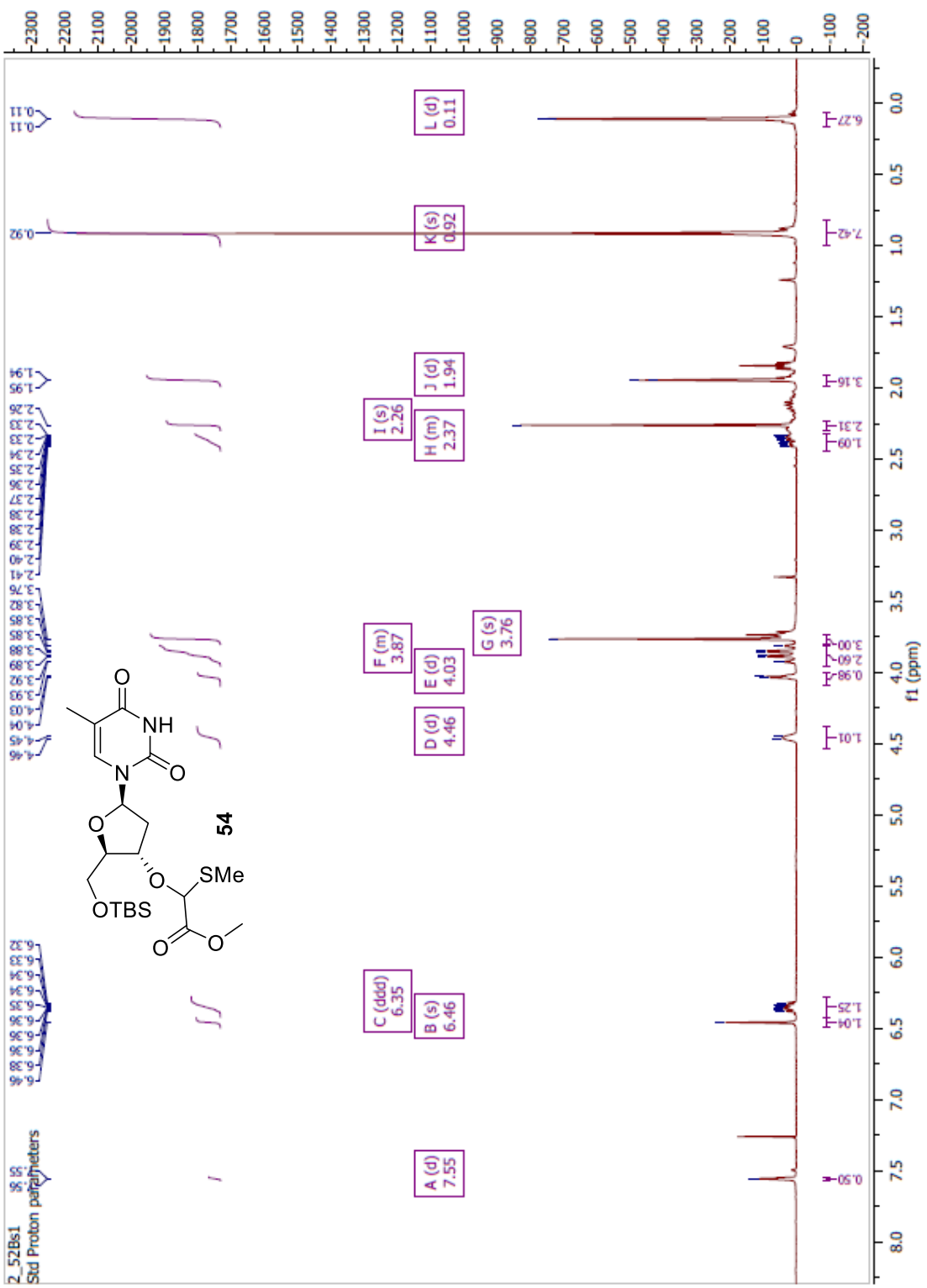

O
NBn
N
O
O
OTBS
ODMTr
3_43A
P (s) 0.10
O (s) 0.91
N (s) 1.47
M (s) 1.94
L (m) 2.32
K (m) 3.38
J (d) 3.78
I (d) 4.01
H (m) 4.51
G (s) 5.11
F (s) 5.28
E (m) 7.03
D (m) 7.27
C (m) 7.46
B (m) 6.82
A (m) 6.41
f1 (ppm)

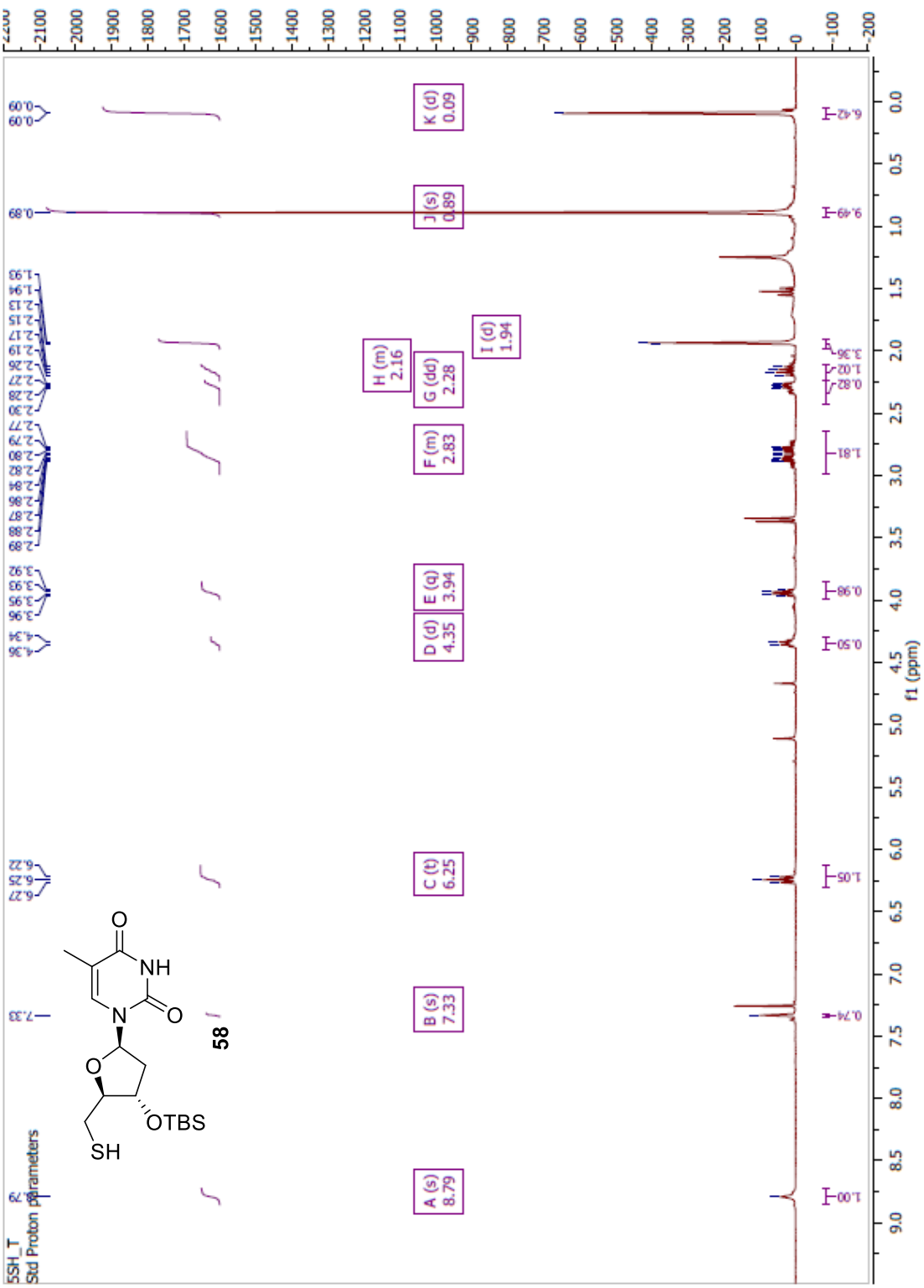

45
NBn
OTBS
Cl
Cl
A (m) 7.47
B (d) 7.26
C (dd) 6.42
D (s) 5.95
E (d) 5.37
F (s) 5.12
G (s) 4.14
H (d) 3.92
I (dd) 2.51
J (ddd) 2.16
K (d) 1.94
L (s) 1.25
M (m) 0.92
N (d) 0.13
O (d) 0.06
f1 (ppm)

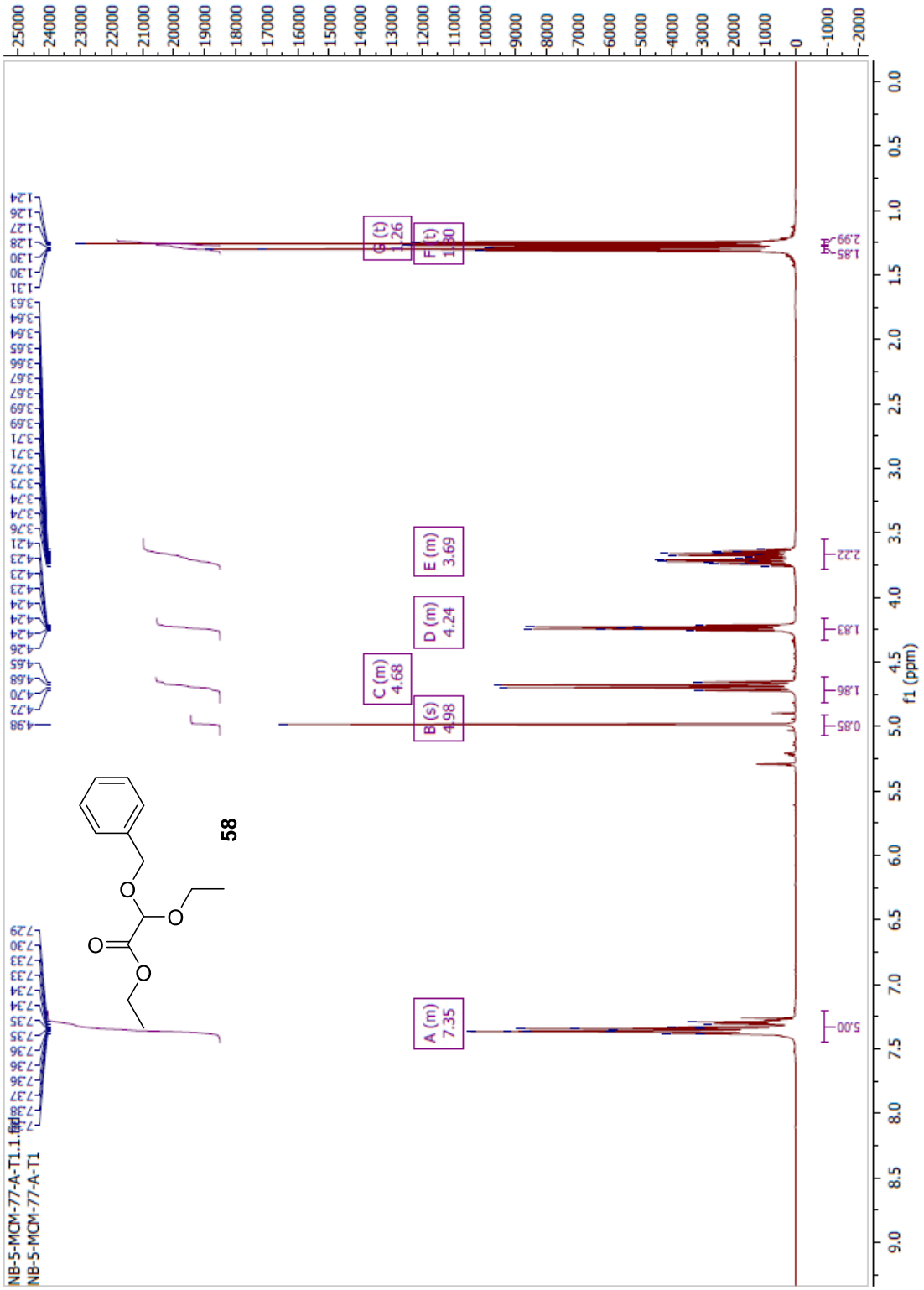

51Acar
Std Carbon experiment
f1 (ppm)
0.00
0.14
6.55
18.84
23.82
31.42
35.23
50.09
69.00
69.35
84.18
90.18
90.74
116.24
133.15
133.90
134.73
138.38
142.31
156.46
168.78
169.70
NBn
O
N
O
O
O
O
Cl
Cl
OTBS
45

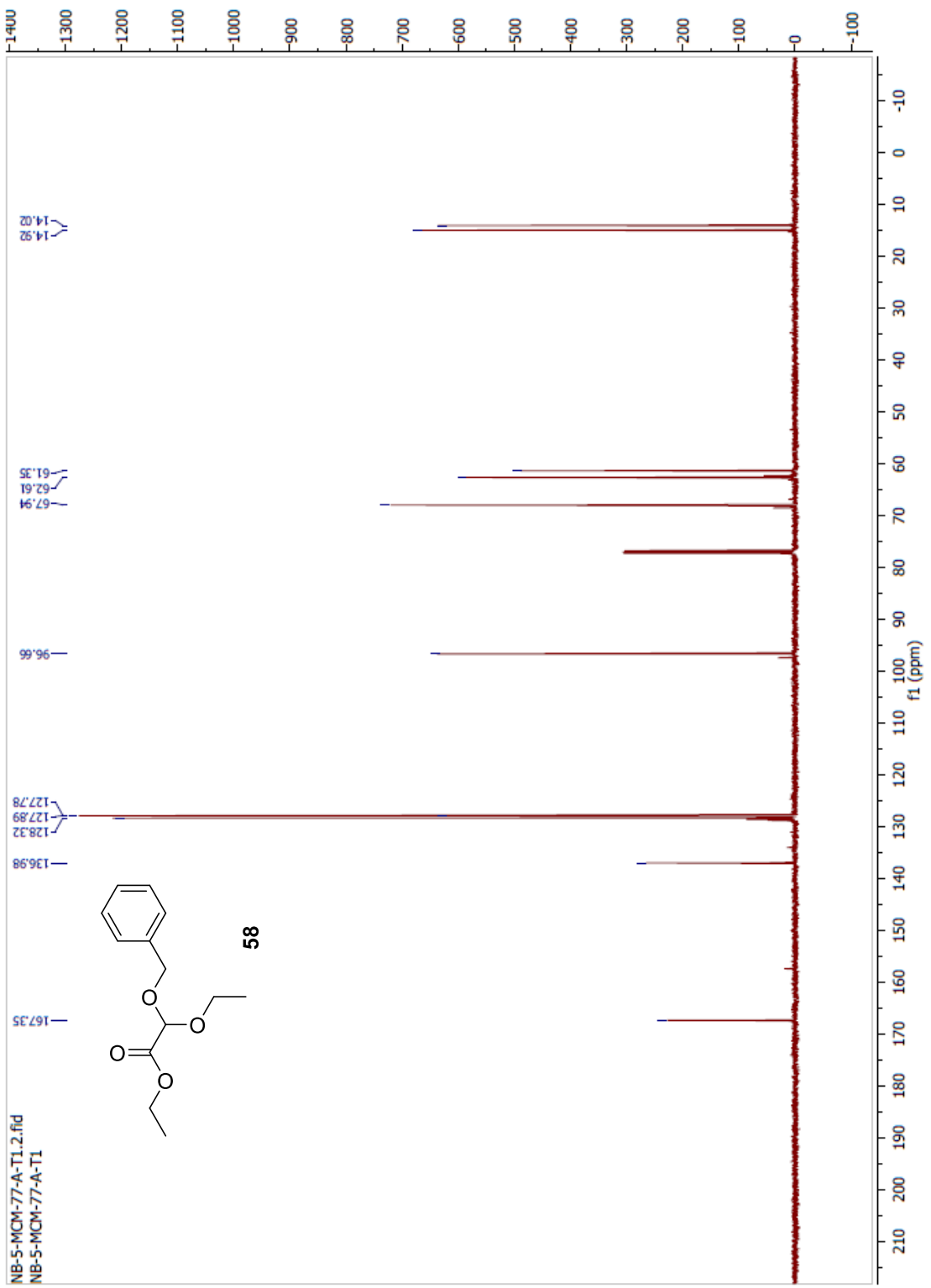

95As2
Std Proton parameters
A (s) 8.30
B (s) 7.58
C (dd) 6.38
D (dd) 5.93
E (d) 5.37
F (s) 4.20
G (m) 3.94
H (dd) 2.51
I (s) 1.92
J (d) 0.93
K (s) 0.13
f1 (ppm)
NH
O
N
O
O
O
Cl
N
OTBS
46

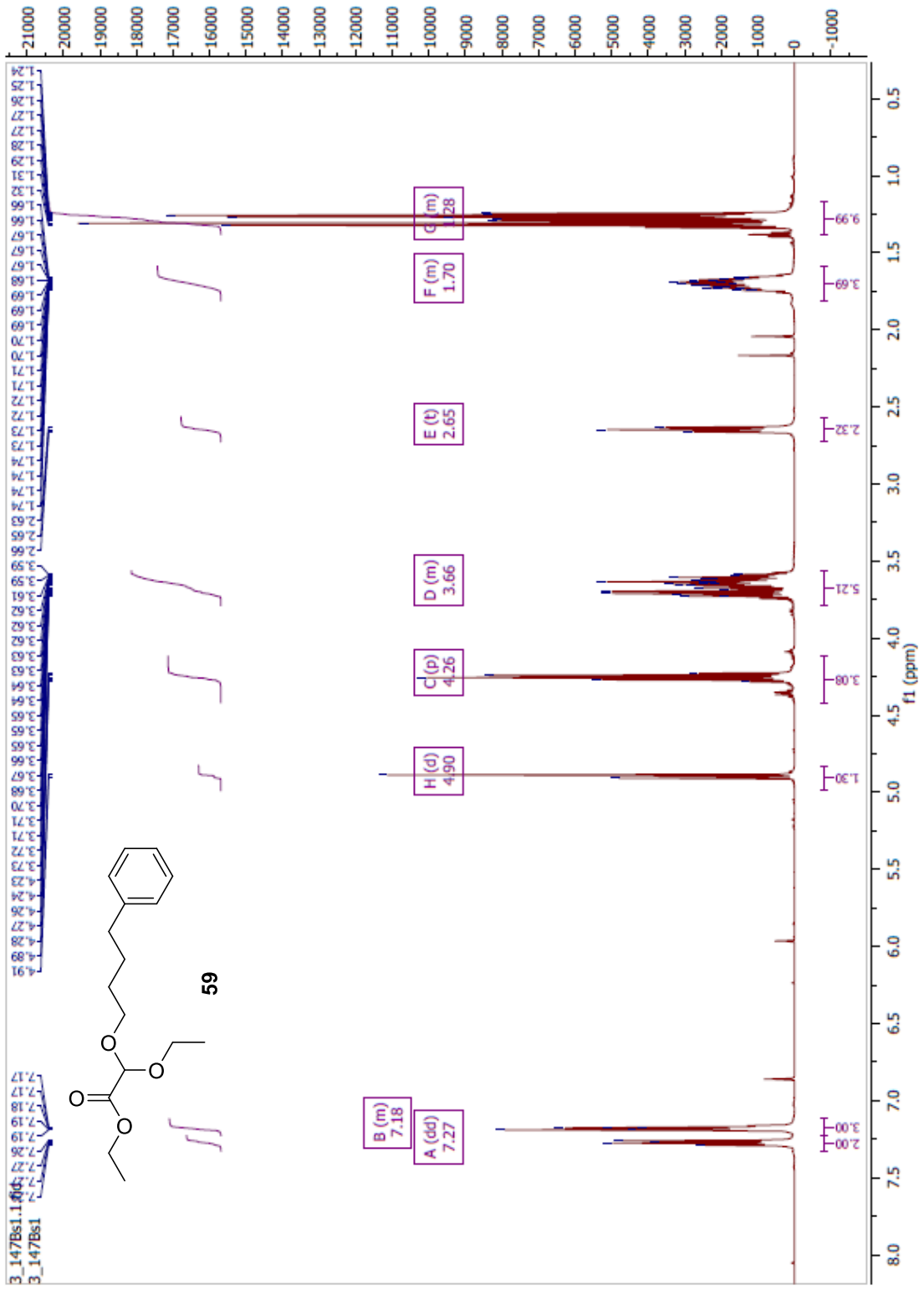

95As2car
Std Carbon experiment
f1 (ppm)
-5.37
-5.46
12.51
18.35
25.93
37.98
65.27
78.56
85.01
84.70
111.20
135.14
164.45
NH
N
O
O
O
O
O
Cl
OTBS
N
46

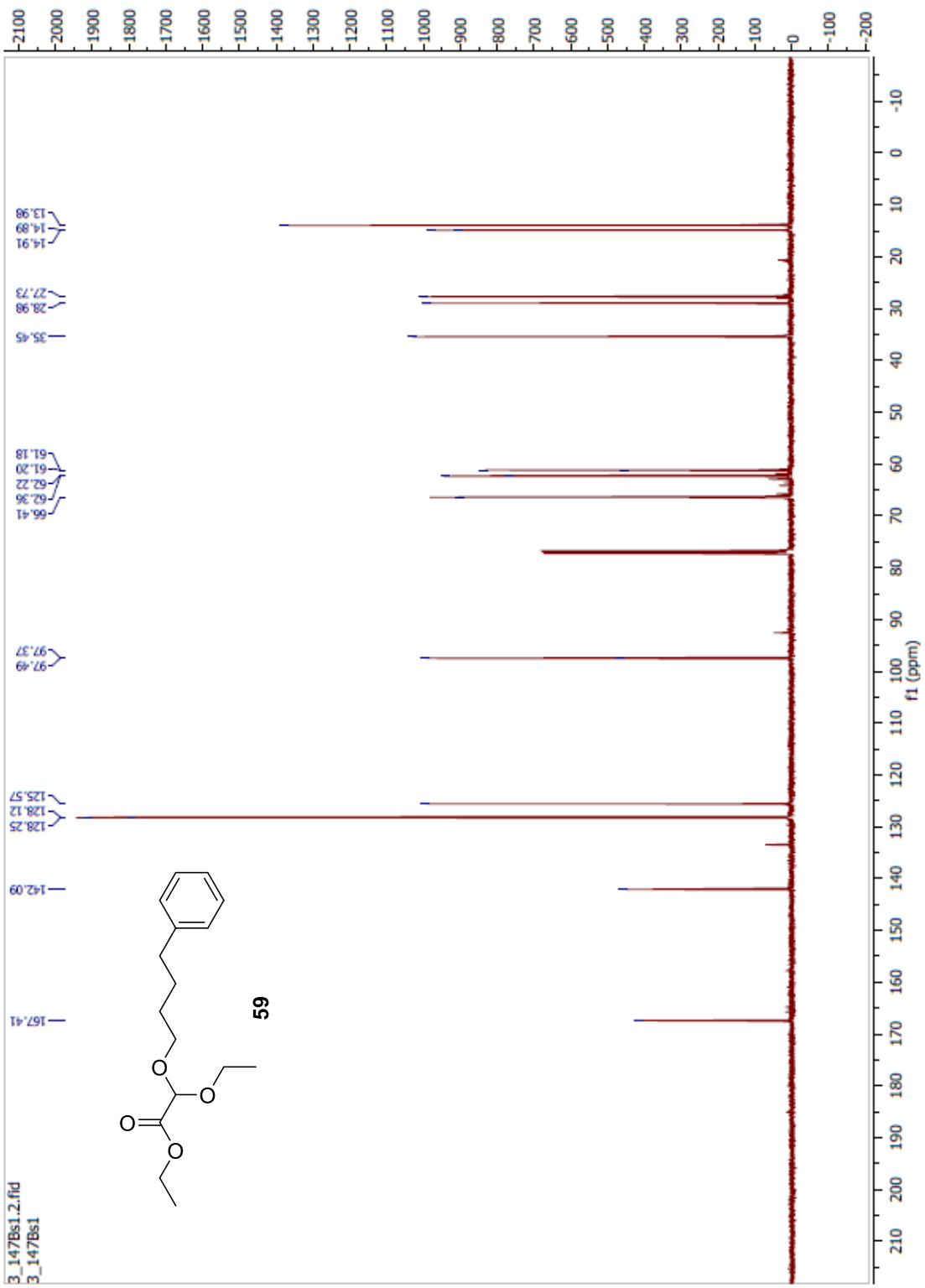

2_52Bs1
Std Proton parameters
A (d) 7.55
B (s) 6.46
C (ddd) 6.35
D (d) 4.46
E (d) 4.03
F (m) 3.87
G (s) 3.76
H (m) 2.37
I (s) 2.26
J (d) 1.94
K (s) 0.92
L (d) 0.11
NH
O
N
O
O
O
SMe
OTBS
O
O
54
f1 (ppm)

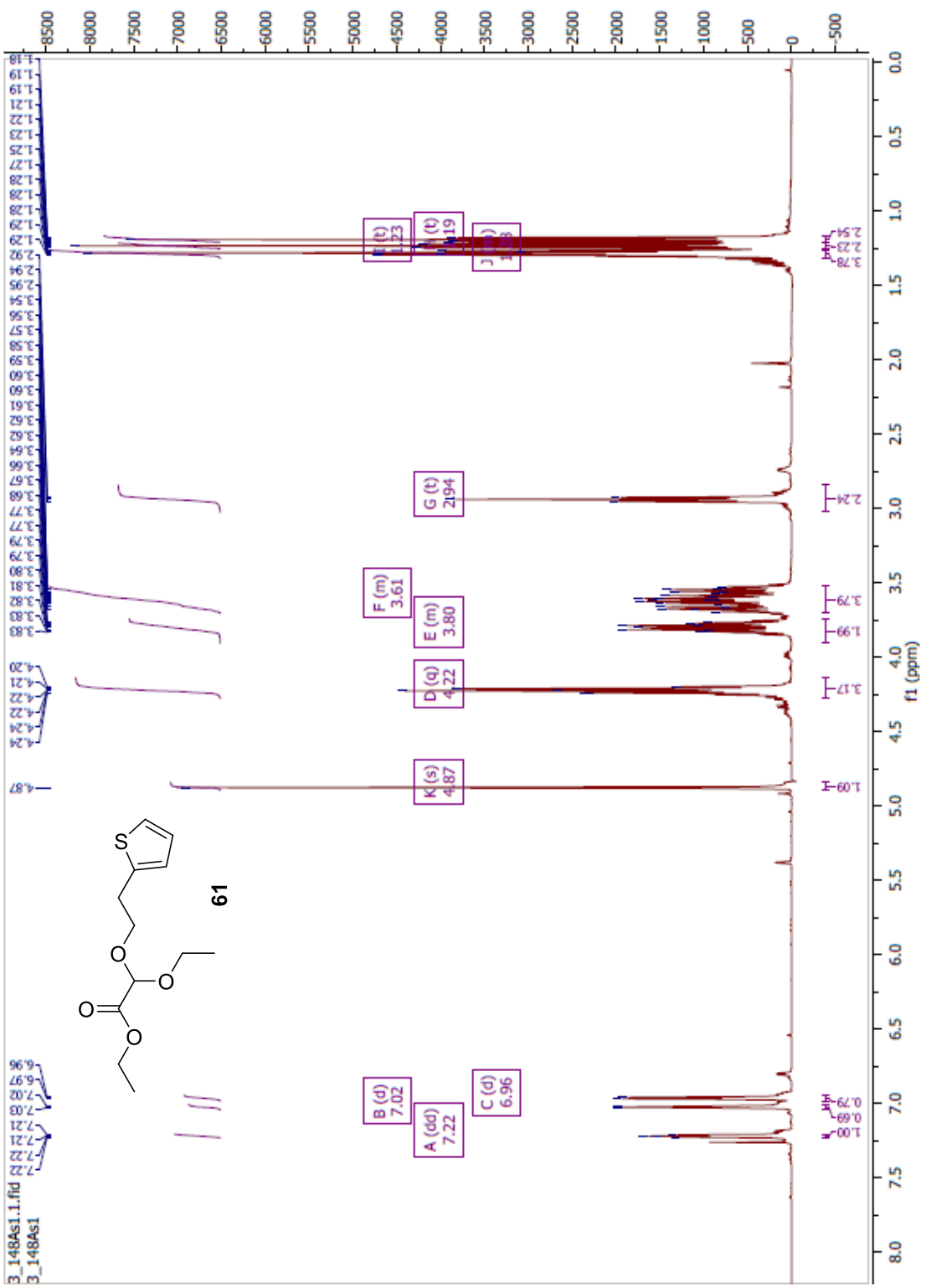

5SH_T
Std Proton parameters
A (s) 8.79
B (s) 7.33
C (t) 6.25
D (d) 4.35
E (q) 3.94
F (m) 2.83
G (dd) 2.28
H (m) 2.16
I (d) 1.94
J (s) 0.89
K (d) 0.09
f1 (ppm)
58
NH
O
O
N
O
OTBS
SH

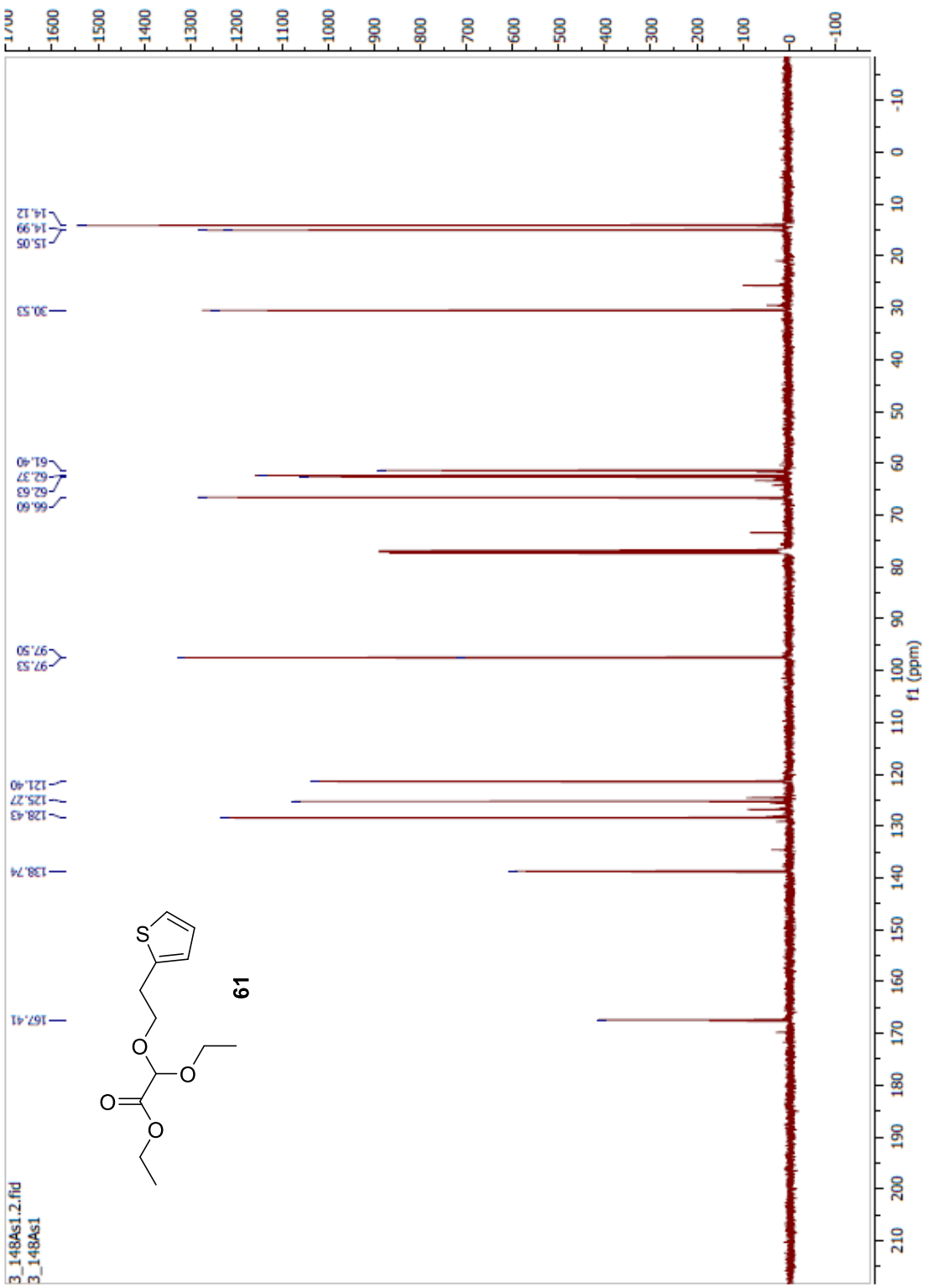

NB-5-MCM-77-A-T1.1.1.fid
NB-5-MCM-77-A-T1
58
A (m) 7.35
B (s) 4.98
C (m) 4.68
D (m) 4.24
E (m) 3.69
F (t) 1.30
G (t) 1.26
5.00
0.85
1.86
1.83
2.22
2.99
1.85
f1 (ppm)

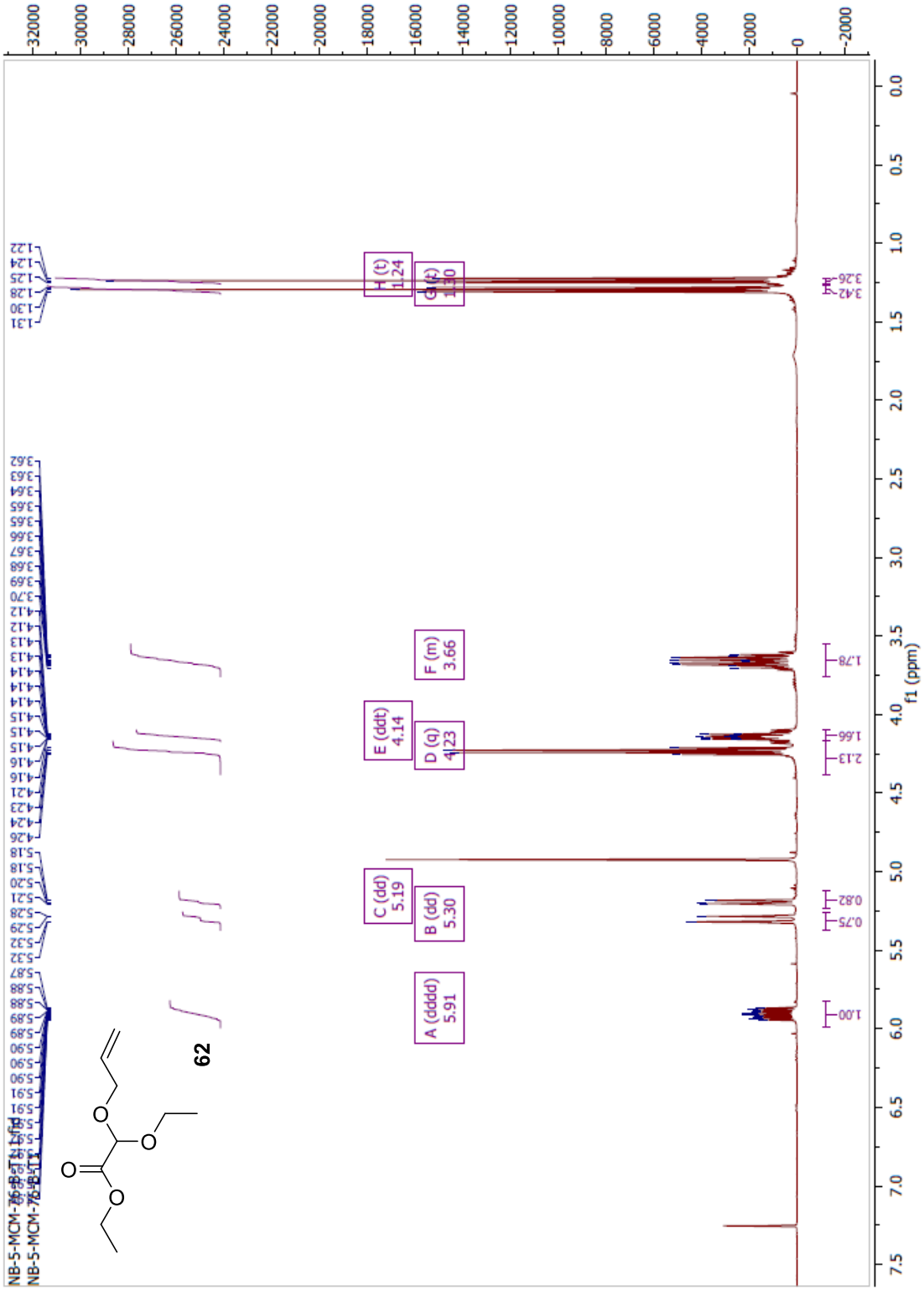

NB-5-MCM-77-A-T1.2.fid
NB-5-MCM-77-A-T1
14.92
14.02
61.35
62.61
67.94
96.66
127.78
127.89
128.32
136.98
167.35
f1 (ppm)
58

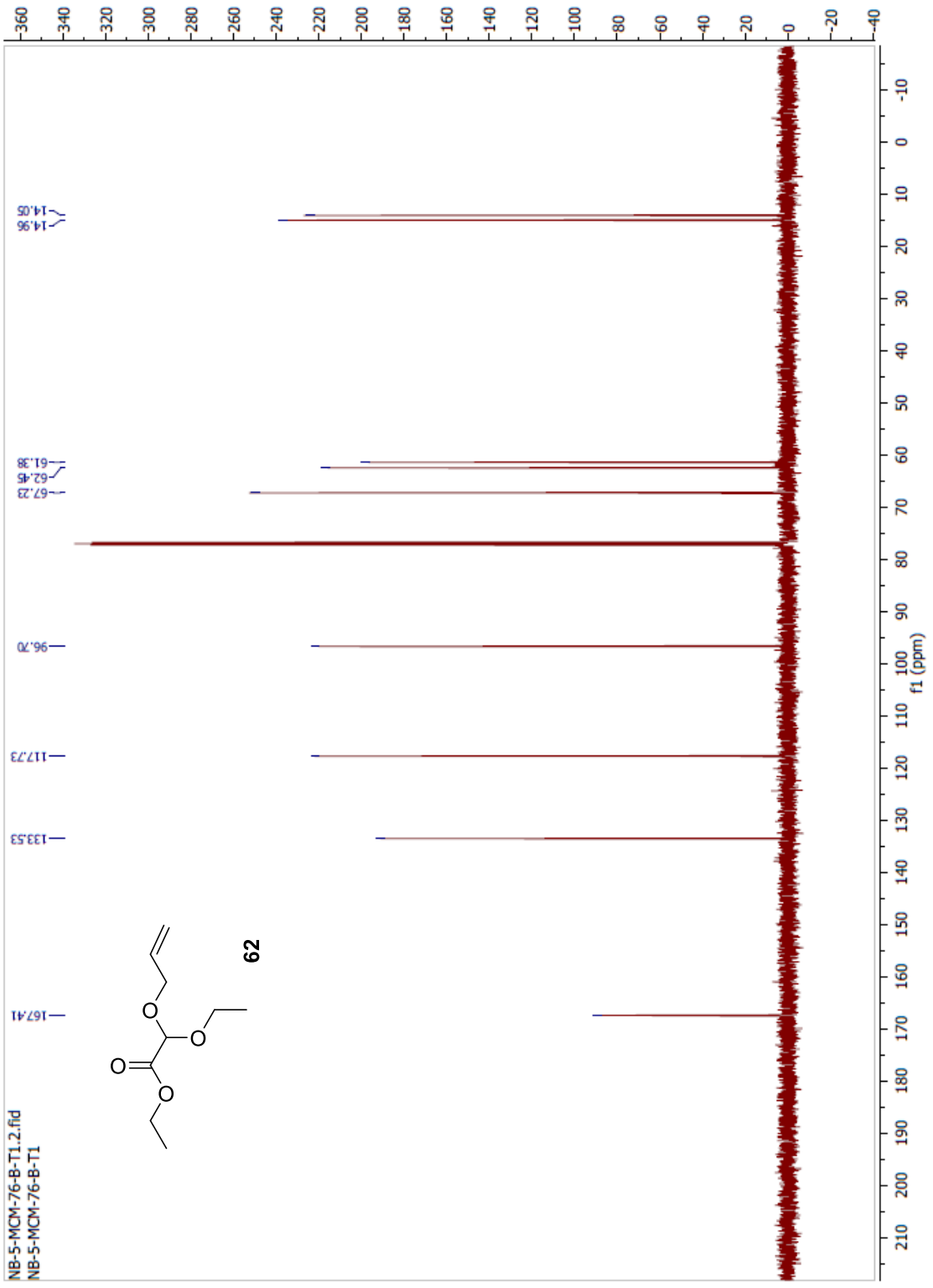

59
A (dd) 7.27
B (m) 7.18
H (d) 4.90
C(p) 4.26
D (m) 3.66
E (t) 2.65
F (m) 1.70
G (m) 1.28
2.00
3.00
1.30
3.08
5.21
2.32
3.69
9.99
f1 (ppm)

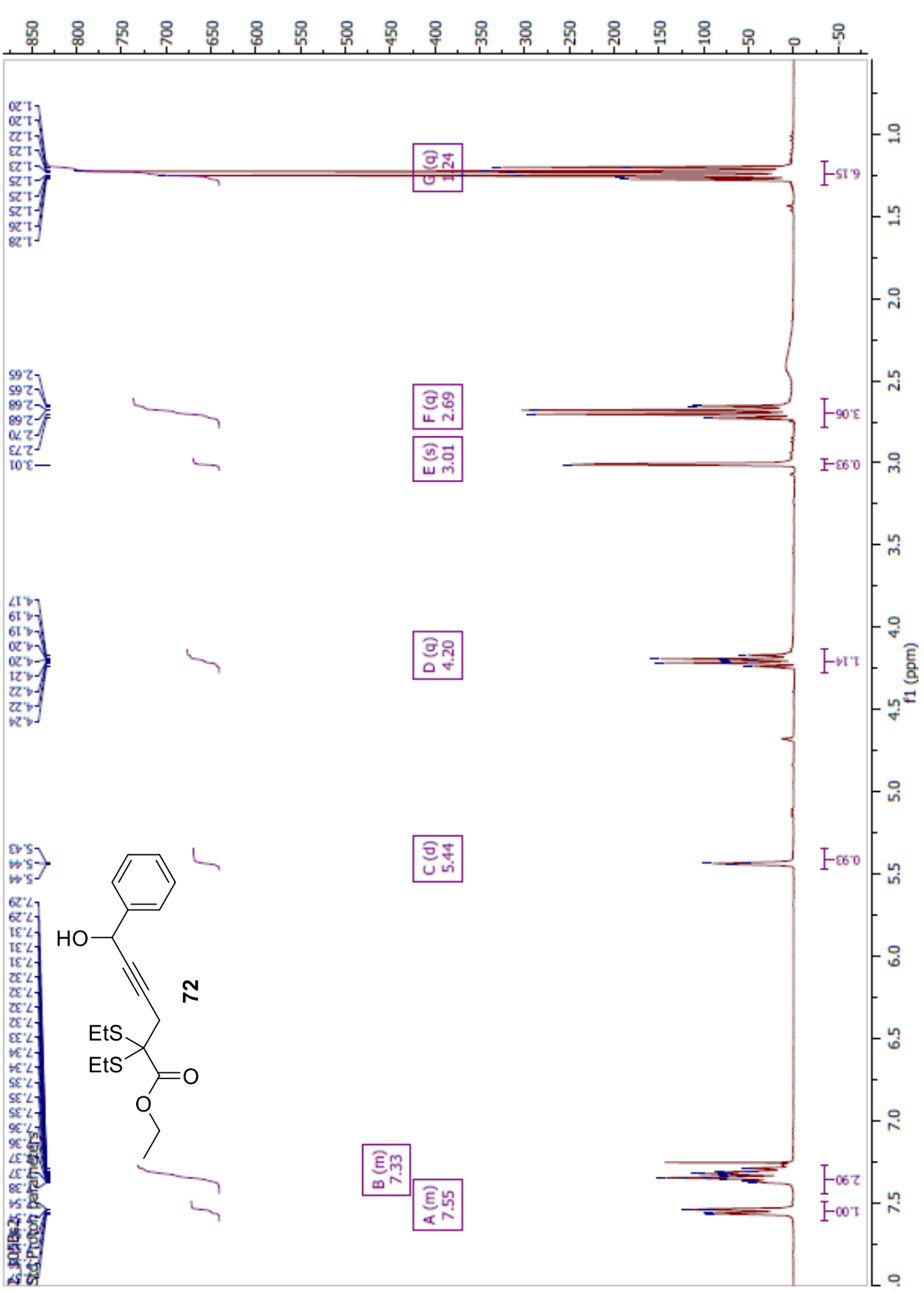

13.98
14.89
14.91
27.73
28.98
35.45
61.18
61.20
62.22
62.36
66.41
97.37
97.49
125.57
128.12
128.25
142.09
167.41
59
f1 (ppm)
3_147Bs1.2.fid
3_147Bs1

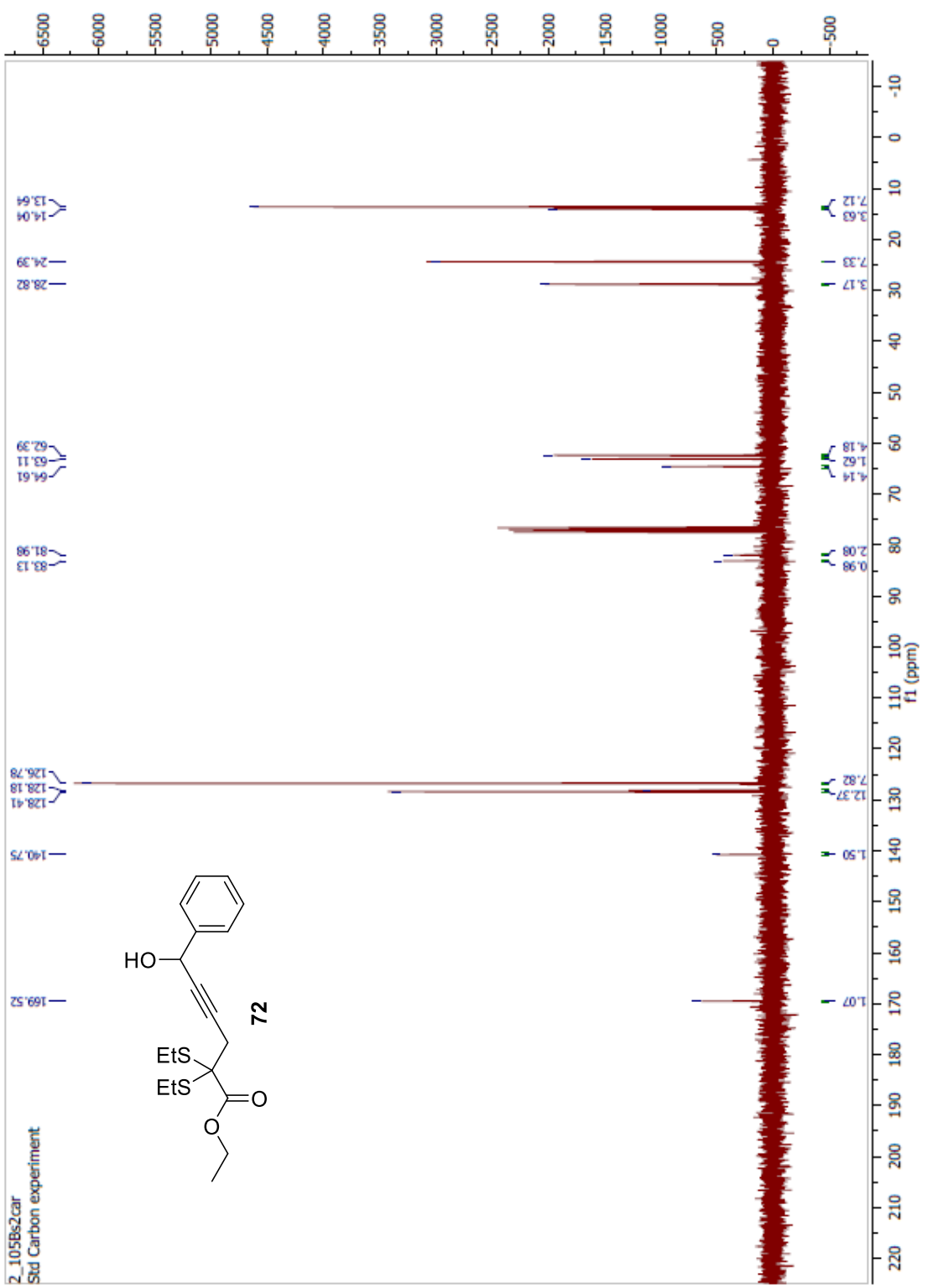

61
A (dd) 7.22
B (d) 7.02
C (d) 6.96
D (q) 4.22
E (m) 3.80
F (m) 3.61
G (t) 2.94
K (s) 4.87
f1 (ppm)

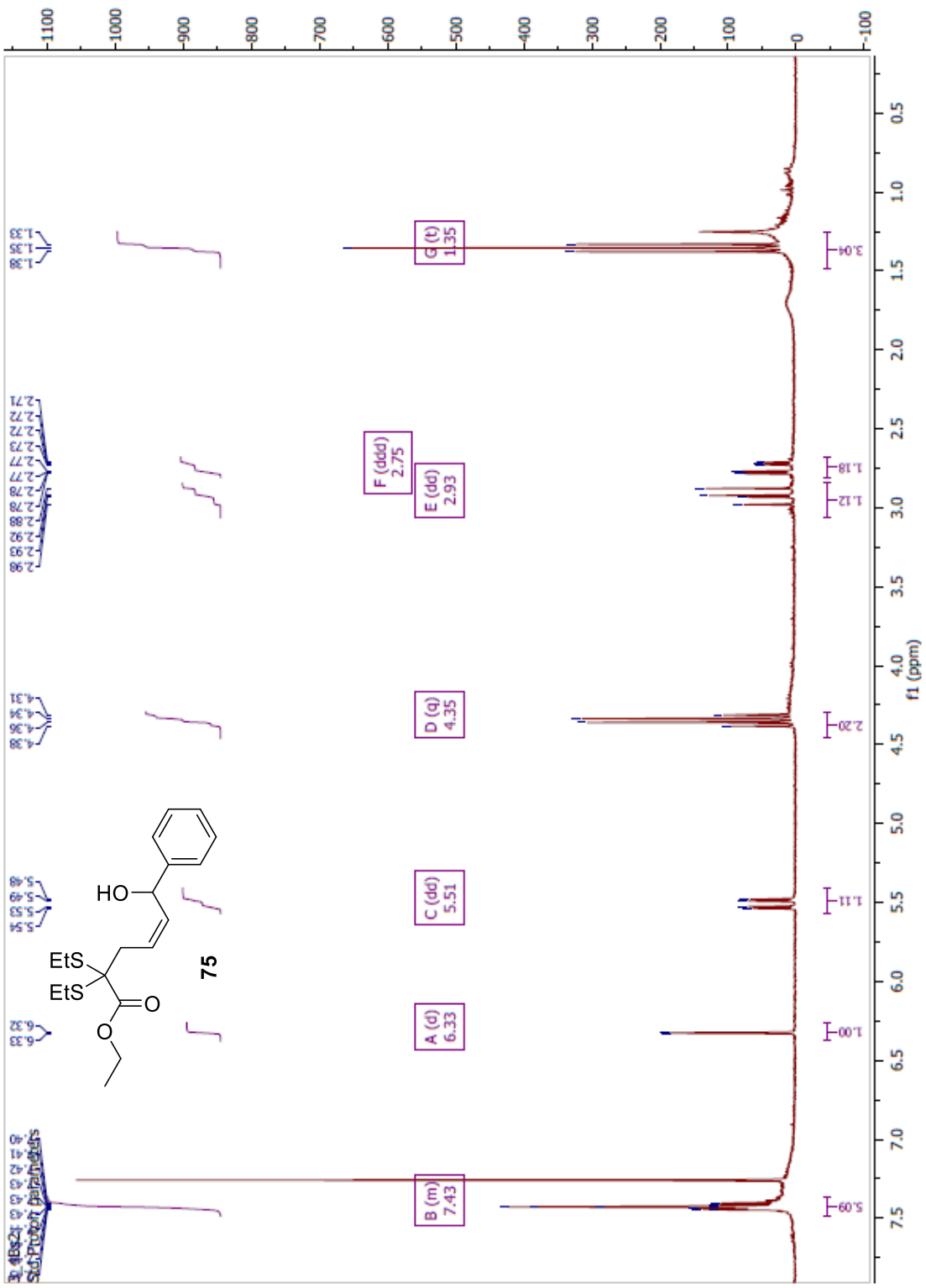

15.05
14.99
14.12
30.53
66.60
62.63
62.37
61.40
97.53
97.50
128.43
125.27
121.40
138.74
167.41
61
f1 (ppm)
3_148As1.2.fid
3_148As1

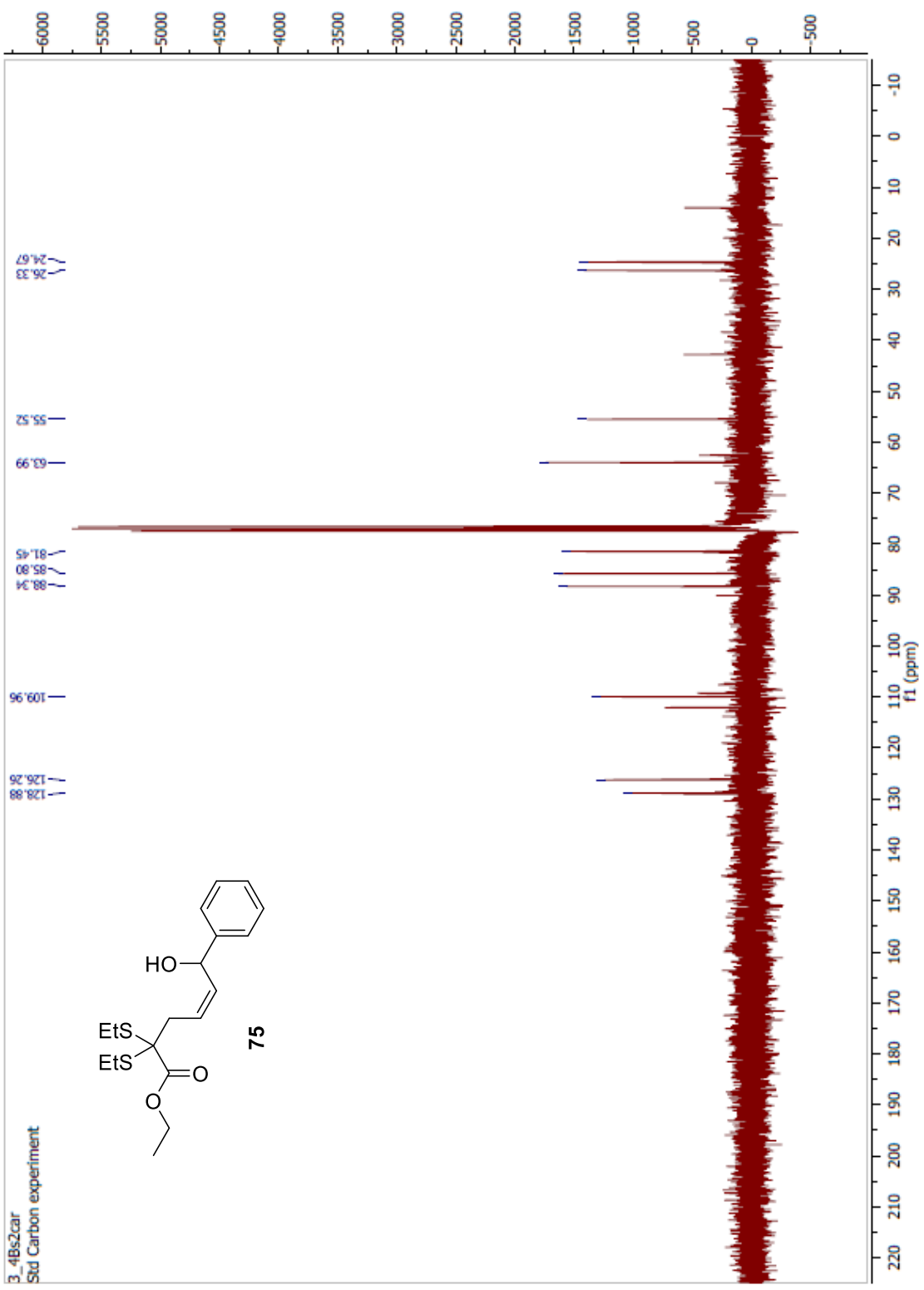

62
A (dddd) 5.91
B (dd) 5.30
C (dd) 5.19
D (q) 4.23
E (ddt) 4.14
F (m) 3.66
G (t) 1.30
H (t) 1.24
1.00
0.75
0.82
2.13
1.66
1.78
3.26
3.42
f1 (ppm)

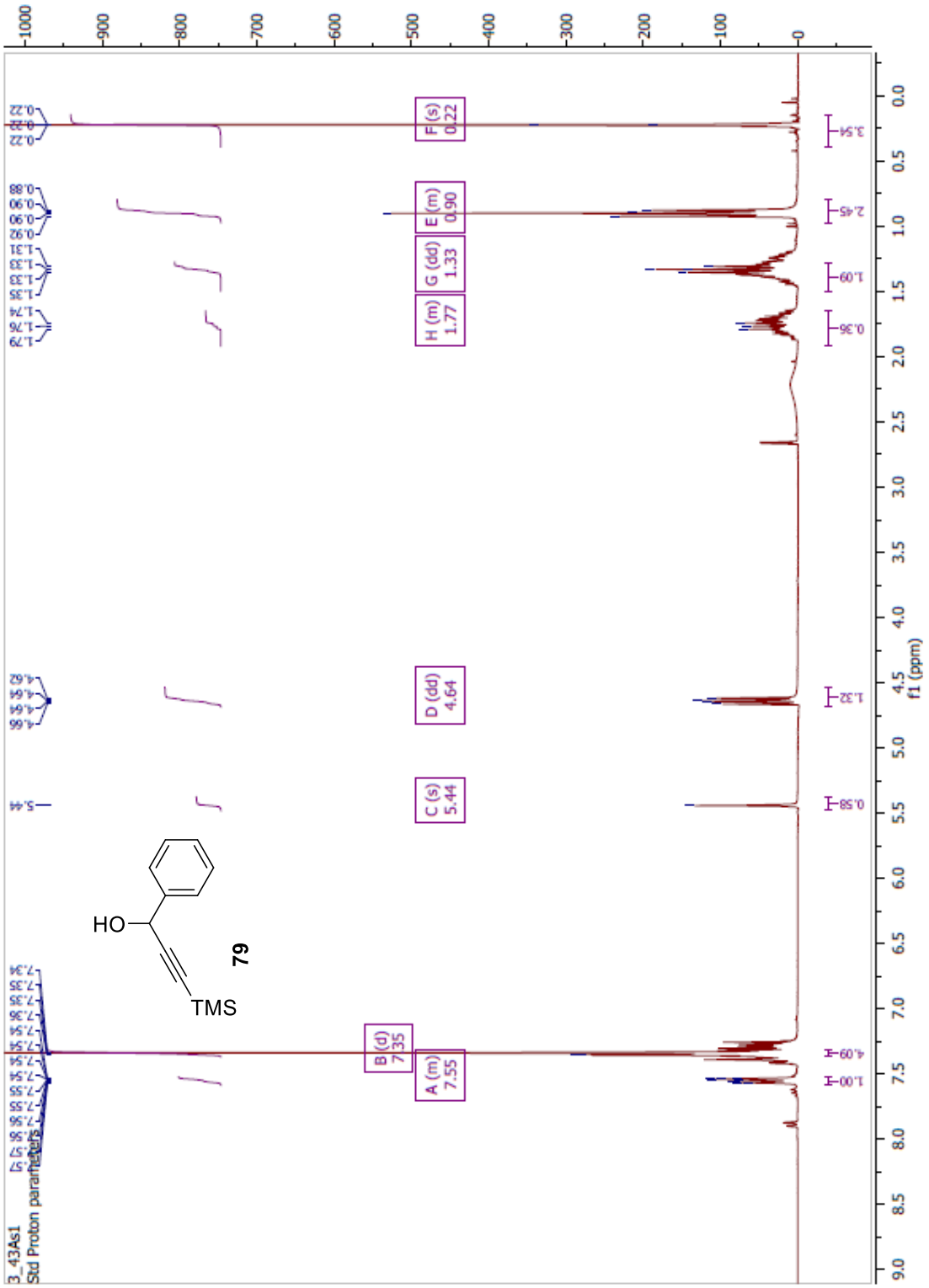

NB-5-MCM-76-B-T1.2.fid
NB-5-MCM-76-B-T1
14.05
14.96
61.38
62.45
67.23
96.70
117.73
133.53
167.41
62
f1 (ppm)

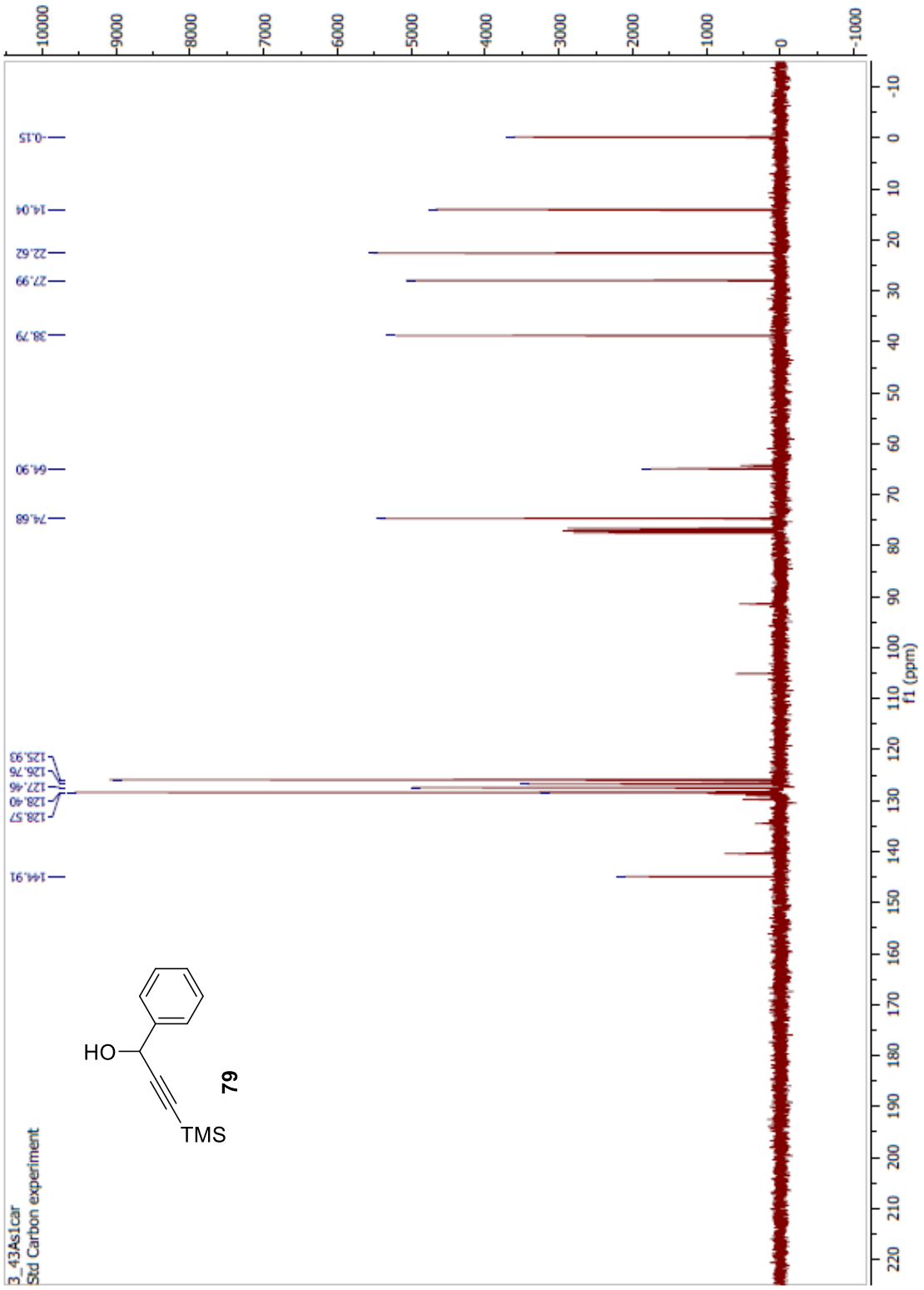

HO
EtS
EtS
O
O
72
A (m) 7.55
B (m) 7.33
C (d) 5.44
D (q) 4.20
E (s) 3.01
F (q) 2.69
G (q) 1.24
f1 (ppm)

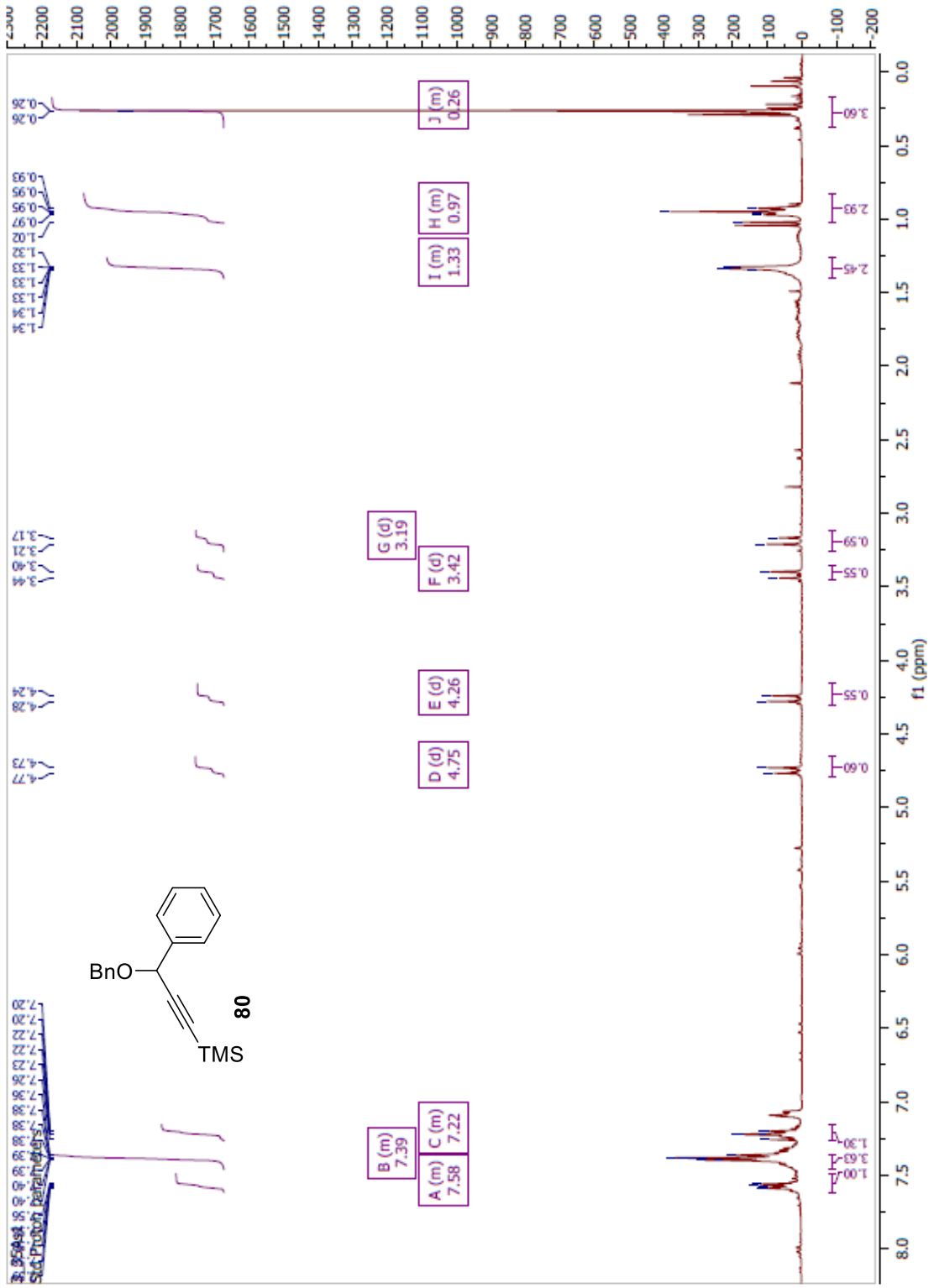

2_105Bs2car
Std Carbon experiment
f1 (ppm)
HO
EtS
EtS
O
O
72

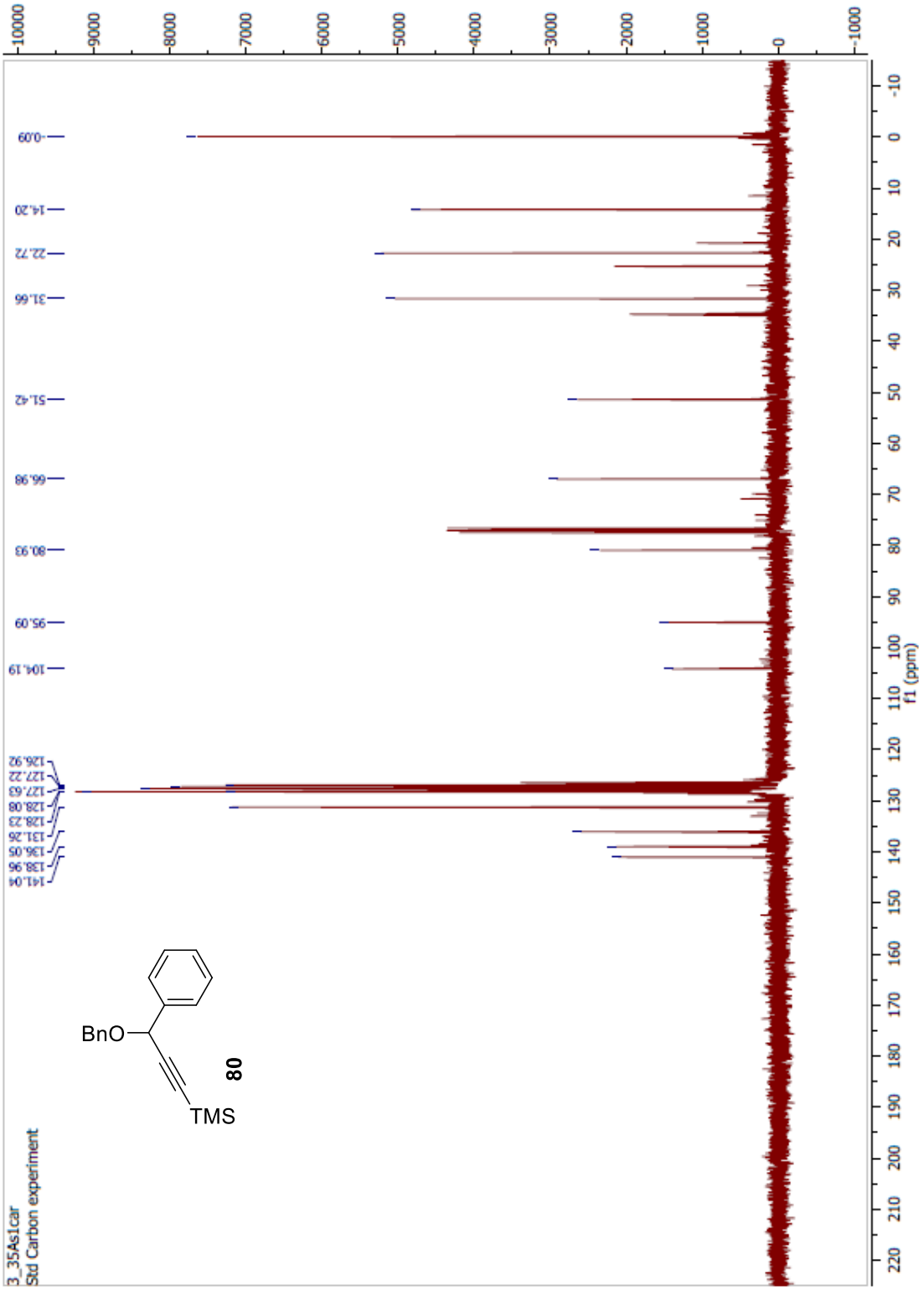

HO
EtS
EtS
O
O
75
A (d) 6.33
B (m) 7.43
C (dd) 5.51
D (q) 4.35
E (dd) 2.93
F (ddd) 2.75
G (t) 1.35
f1 (ppm)

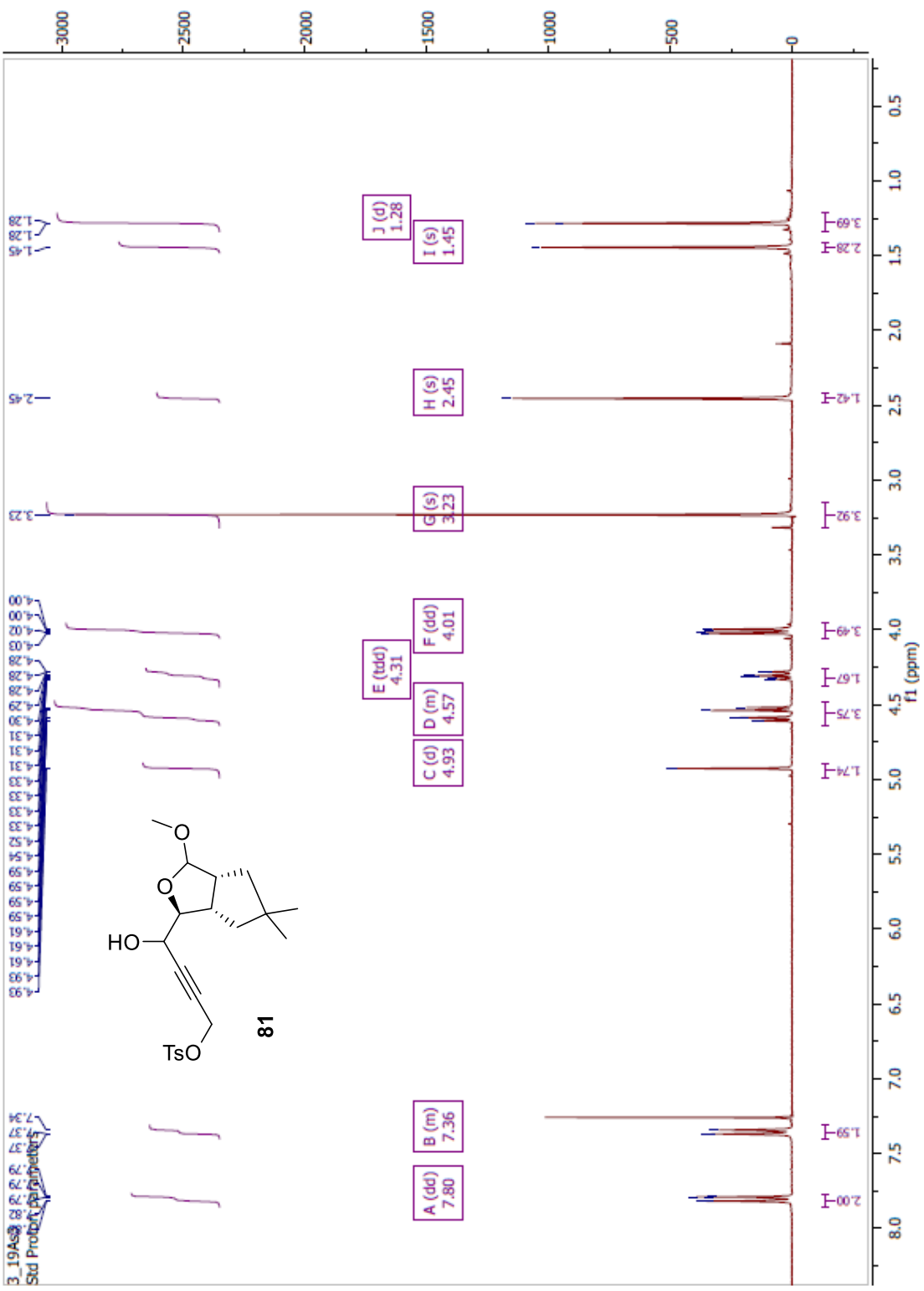

3_4Bs2car
Std Carbon experiment
f1 (ppm)
24.67
26.33
55.52
63.99
81.45
85.80
88.34
109.96
126.26
128.88
HO
EtS
EtS
O
O
75

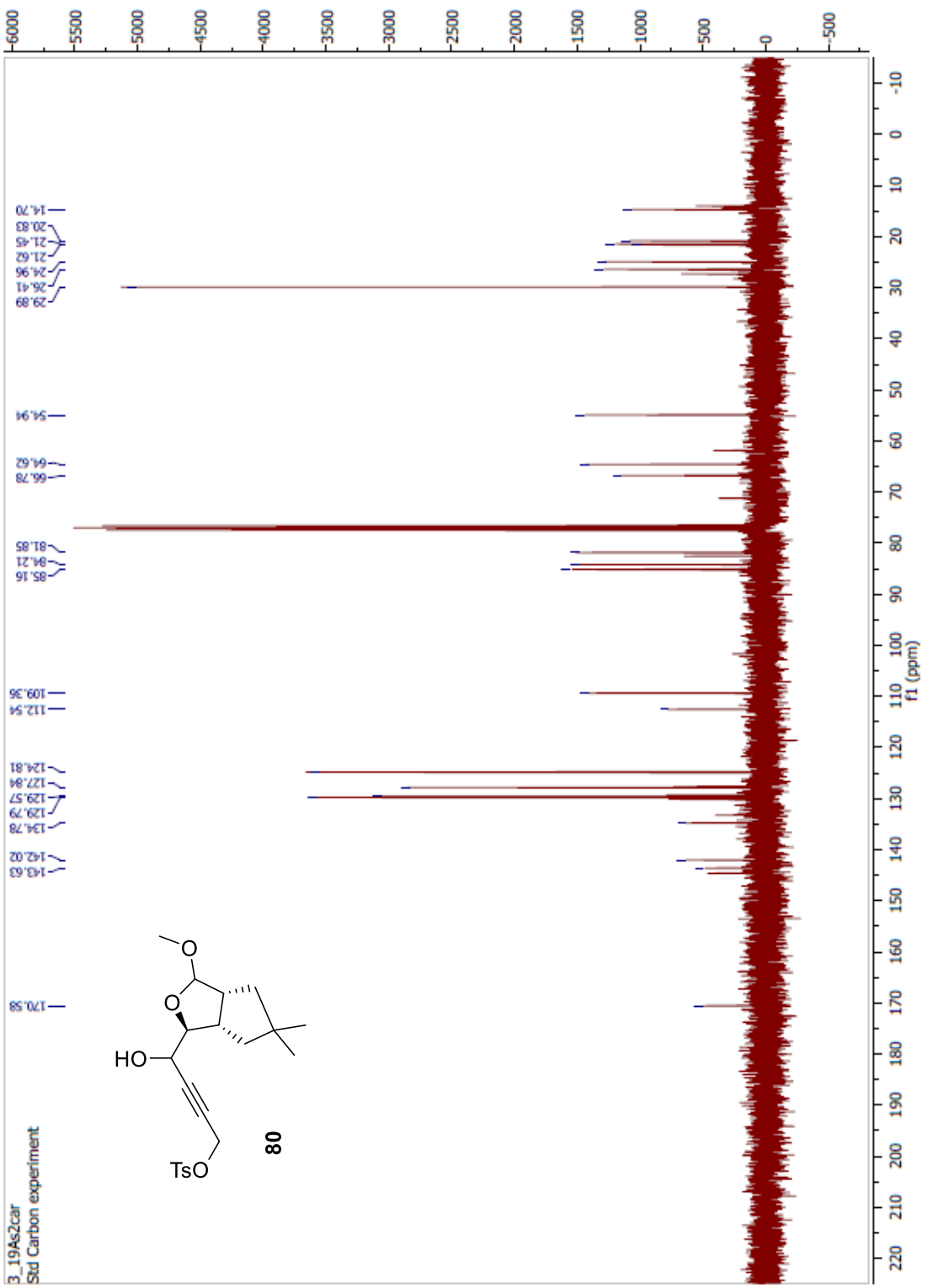

HO
TMS
79
A (m) 7.55
B (d) 7.35
C (s) 5.44
D (dd) 4.64
E (m) 0.90
F (s) 0.22
G (dd) 1.33
H (m) 1.77
f1 (ppm)

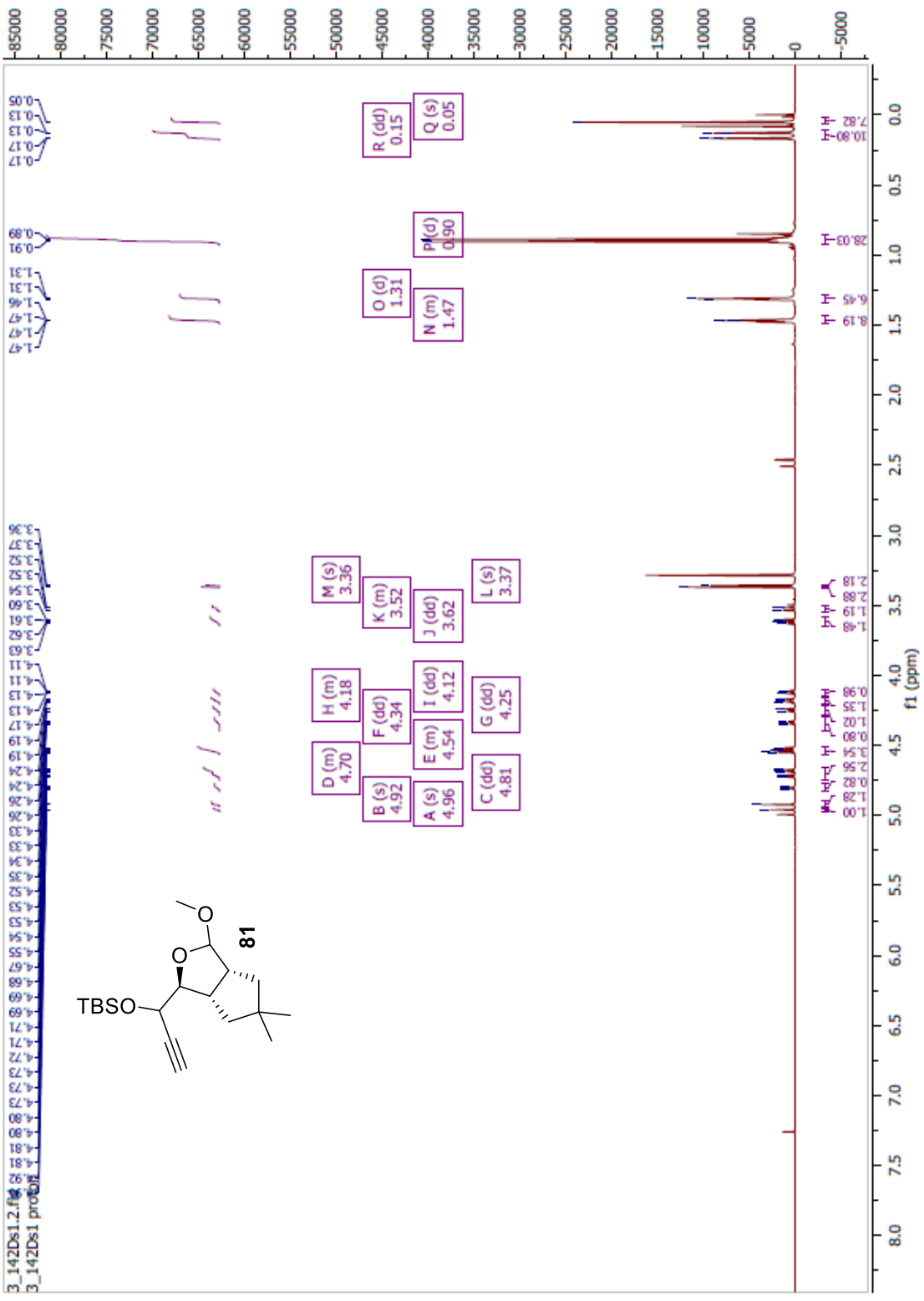

-0.15
14.04
22.62
27.99
38.79
64.90
74.68
125.93
126.76
127.46
128.40
128.57
144.91
HO
TMS
79
3_43As1car
Std Carbon experiment
f1 (ppm)

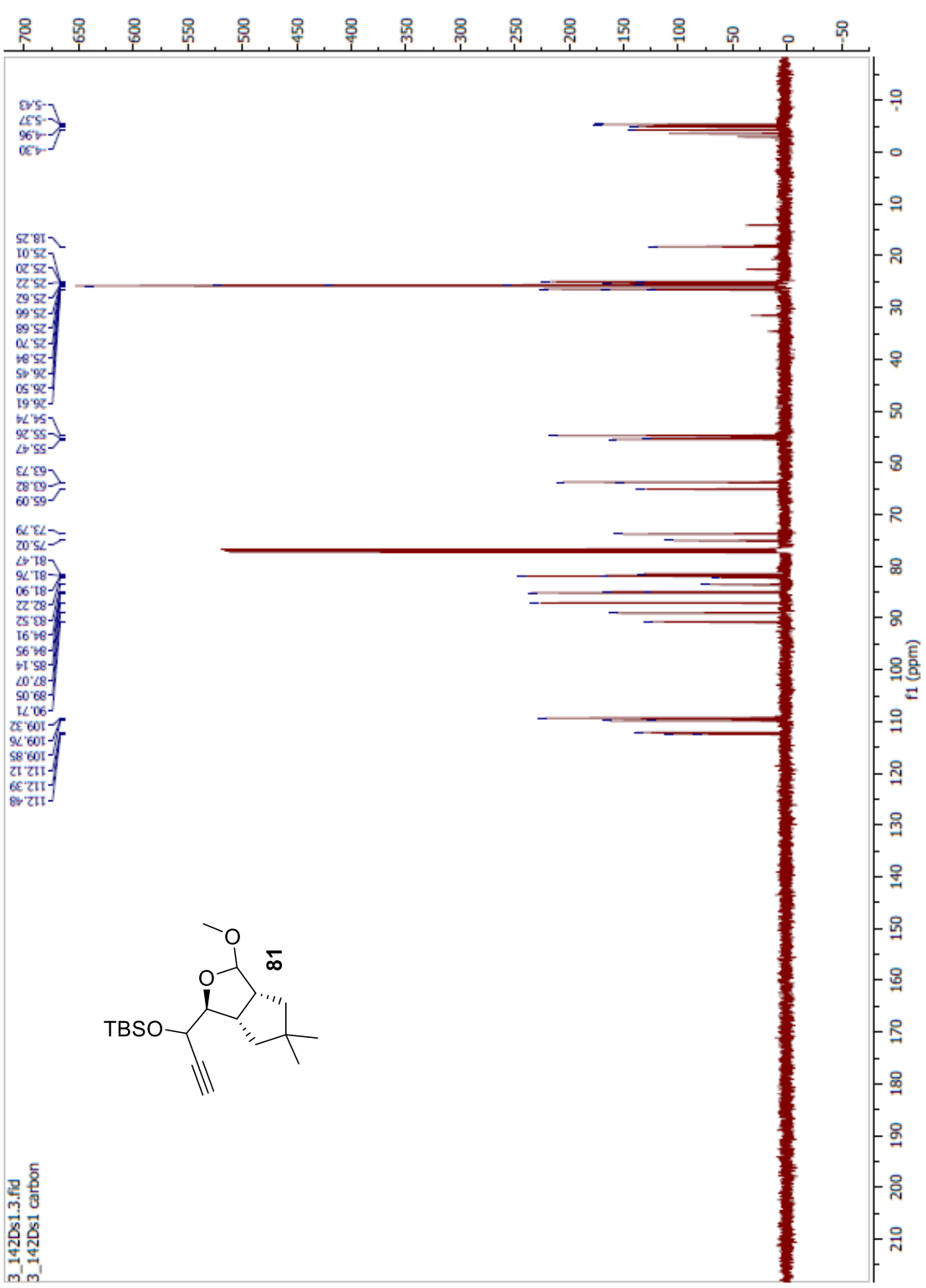

BnO
TMS
80
A (m) 7.58
B (m) 7.39
C (m) 7.22
D (d) 4.75
E (d) 4.26
F (d) 3.42
G (d) 3.19
H (m) 0.97
I (m) 1.33
J (m) 0.26
f1 (ppm)

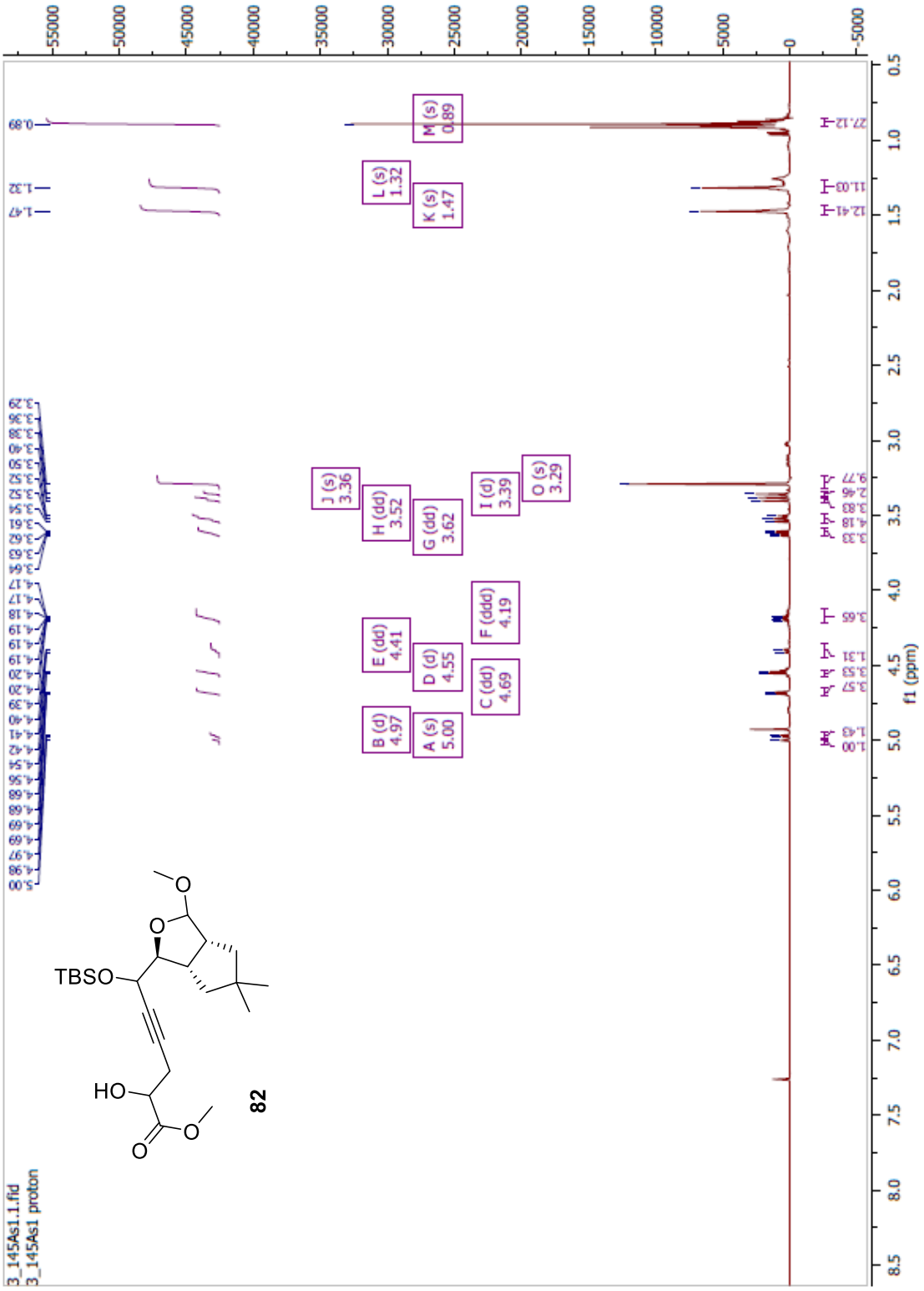

-0.09
14.20
22.72
31.66
51.42
66.98
80.93
95.09
104.19
126.92
127.22
127.63
128.08
128.23
131.26
136.05
138.96
141.04
BnO
TMS
80
f1 (ppm)
3_35As1car
Std Carbon experiment

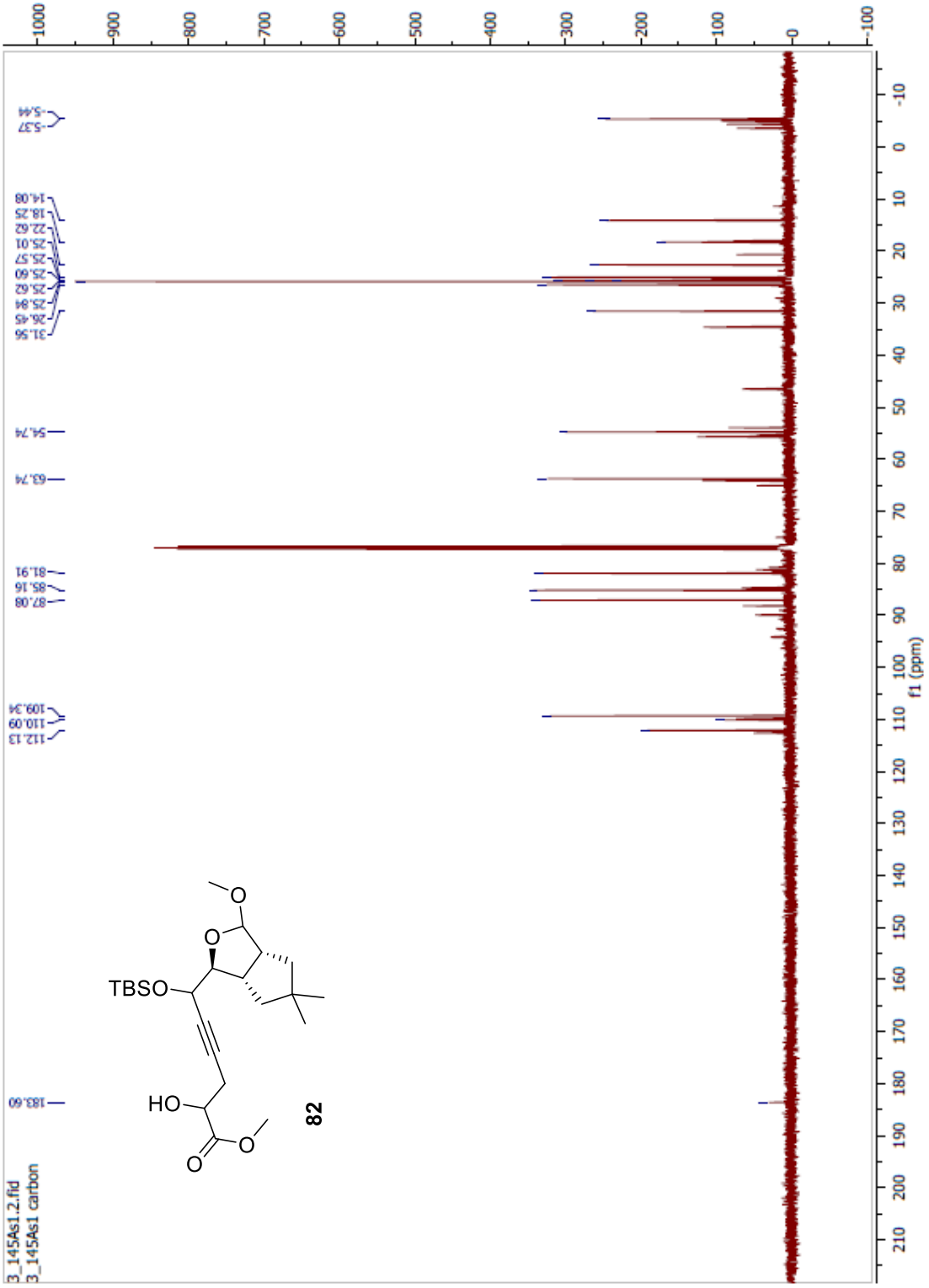

A (dd) 7.80
B (m) 7.36
C (d) 4.93
D (m) 4.57
E (tdd) 4.31
F (dd) 4.01
G (s) 3.23
H (s) 2.45
I (s) 1.45
J (d) 1.28
HO
O
O
TsO
81
f1 (ppm)


3_19As2car
Std Carbon experiment
14.70
20.83
21.45
21.62
24.96
26.41
29.89
54.94
64.62
66.78
81.85
84.21
85.16
109.36
112.54
124.81
127.84
129.57
129.79
134.78
142.02
143.63
170.58
HO
O
O
TsO
80
f1 (ppm)


TBSO
O
O
81
A (s) 4.96
B (s) 4.92
C (dd) 4.81
D (m) 4.70
E (m) 4.54
F (dd) 4.34
G (dd) 4.25
H (m) 4.18
I (dd) 4.12
J (dd) 3.62
K (m) 3.52
L (s) 3.37
M (s) 3.36
N (m) 1.47
O (d) 1.31
P (d) 0.90
Q (s) 0.05
R (dd) 0.15
f1 (ppm)


3_142Ds1.3.fid
3_142Ds1 carbon
f1 (ppm)
TBSO
O
O
81


TBSO
HO
O
O
O
O
82
M (s) 0.89
L (s) 1.32
K (s) 1.47
J (s) 3.36
H (dd) 3.52
G (dd) 3.62
I (d) 3.39
O (s) 3.29
F (ddd) 4.19
E (dd) 4.41
D (d) 4.55
C (dd) 4.69
B (d) 4.97
A (s) 5.00
f1 (ppm)


-5.37
-5.44
14.08
18.25
22.62
25.01
25.57
25.60
25.62
25.84
26.45
31.56
54.74
63.74
81.91
85.16
87.08
109.34
110.09
112.13
183.60
TBSO
HO
O
O
O
O
82
f1 (ppm)
3_145As1.2.fid
3_145As1 carbon

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